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(54) Title: STE20-RELATED PROTEIN KINASES			
(57) Abstract  The present invention relates to the novel kinase polypeptides STLK2, STLK3, STLK4, STLK5, STLK6, STLK7, ZC1, ZC2, ZC3, ZC4, KHS2, SULU1, SULU3, GEK2, PAK4, and PAK5, nucleotide sequences encoding the novel kinase polypeptides, as well as various products and methods useful for the diagnosis and treatment of various kinase-related diseases and conditions.			

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DESCRIPTION

## STE20-RELATED PROTEIN KINASES

RELATED APPLICATIONS

5 The present application claims priority to U.S. Provisional Patent Application Serial No. 60/081,784 by Plowman and Martinez, entitled STE20-Related Protein kinases, filed April 14, 1998 (Lyon & Lyon Docket No. 10 232/279), hereby incorporated by reference herein in its entirety, including any drawings, tables, or figures.

FIELD OF THE INVENTION

15 The present invention relates to novel kinase polypeptides, nucleotide sequences encoding the novel kinase polypeptides, as well as various products and methods useful for the diagnosis and treatment of various kinase-related diseases and conditions.

BACKGROUND OF THE INVENTION

20 The following description of the background of the invention is provided to aid in understanding the invention, but is not admitted to be or to describe prior art to the invention.

25 Cellular signal transduction is a fundamental mechanism whereby external stimuli that regulate diverse cellular processes are relayed to the interior of cells. One of the key biochemical mechanisms of signal transduction involves the reversible phosphorylation of proteins, which enables 30 regulation of the activity of mature proteins by altering their structure and function.

The best characterized protein kinases in eukaryotes phosphorylate proteins on the hydroxyl moiety of serine, threonine and tyrosine residues. These kinases largely fall

into two groups, those specific for phosphorylating serines and threonines, and those specific for phosphorylating tyrosines. Some kinases, referred to as "dual specificity" kinases, are able to phosphorylate on tyrosine as well as serine/threonine residues.

Protein kinases can also be characterized by their location within the cell. Some kinases are transmembrane receptor-type proteins capable of directly altering their catalytic activity in response to the external environment such as the binding of a ligand. Others are non-receptor-type proteins lacking any transmembrane domain. They can be found in a variety of cellular compartments from the inner surface of the cell membrane to the nucleus.

Many kinases are involved in regulatory cascades wherein their substrates may include other kinases whose activities are regulated by their phosphorylation state. Ultimately the activity of some downstream effector is modulated by phosphorylation resulting from activation of such a pathway.

Protein kinases are one of the largest families of eukaryotic proteins with several hundred known members. These proteins share a 250-300 amino acid domain that can be subdivided into 12 distinct subdomains that comprise the common catalytic core structure. These conserved protein motifs have recently been exploited using PCR-based cloning strategies leading to a significant expansion of the known kinases.

Multiple alignment of the sequences in the catalytic domain of protein kinases and subsequent parsimony analysis permits the segregation of related kinases into distinct branches or subfamilies including: tyrosine kinases, cyclic-nucleotide-dependent kinases, calcium/calmodulin kinases, cyclin-dependent kinases and MAP-kinases, serine-



threonine kinase receptors, and several other less defined subfamilies.

#### SUMMARY OF THE INVENTION

5 Through the use of a targeted PCR cloning strategy and of a "motif extraction" bioinformatics script, mammalian members of the STE20-kinase family have been identified as part of the present invention. Multiple alignment and parsimony analysis of the catalytic domain of all of these  
10 STE20-family members reveals that these proteins cluster into 9 distinct subgroups. Classification in this manner has proven highly accurate not only in predicting motifs present in the remaining non-catalytic portion of each protein, but also in their regulation, substrates, and  
15 signaling pathways. The present invention includes the partial or complete sequence of new members of the STE20-family, their classification, predicted or deduced protein structure, and a strategy for elucidating their biologic and therapeutic relevance.

20 Thus, a first aspect of the invention features an isolated, enriched, or purified nucleic acid molecule encoding a kinase polypeptide selected from the group consisting of STLK2, STLK3, STLK4, STLK5, STLK6, STLK7, ZC1, ZC2, ZC3, ZC4, KHS2, SULU1, SULU3, GEK2, PAK4, and PAK5.

25 By "isolated" in reference to nucleic acid is meant a polymer of nucleotides conjugated to each other, including DNA and RNA, that is isolated from a natural source or that is synthesized. The isolated nucleic acid of the present invention is unique in the sense that it is not found in a  
30 pure or separated state in nature. Use of the term "isolated" indicates that a naturally occurring sequence has been removed from its normal cellular (*i.e.*, chromosomal) environment. Thus, the sequence may be in a cell-free

solution or placed in a different cellular environment. The term does not imply that the sequence is the only nucleotide chain present, but that it is essentially free (about 90 - 95% pure at least) of non-nucleotide material naturally associated with it, and thus is distinguished from isolated chromosomes.

By the use of the term "enriched" in reference to nucleic acid is meant that the specific DNA or RNA sequence constitutes a significantly higher fraction (2 - 5 fold) of the total DNA or RNA present in the cells or solution of interest than in normal or diseased cells or in the cells from which the sequence was taken. This could be caused by a person by preferential reduction in the amount of other DNA or RNA present, or by a preferential increase in the amount of the specific DNA or RNA sequence, or by a combination of the two. However, it should be noted that enriched does not imply that there are no other DNA or RNA sequences present, just that the relative amount of the sequence of interest has been significantly increased. The term "significant" is used to indicate that the level of increase is useful to the person making such an increase, and generally means an increase relative to other nucleic acids of about at least 2 fold, more preferably at least 5 to 10 fold or even more. The term also does not imply that there is no DNA or RNA from other sources. The other source DNA may, for example, comprise DNA from a yeast or bacterial genome, or a cloning vector such as pUC19. This term distinguishes from naturally occurring events, such as viral infection, or tumor type growths, in which the level of one mRNA may be naturally increased relative to other species of mRNA. That is, the term is meant to cover only those situations in which a person has intervened to elevate the proportion of the desired nucleic acid.

It is also advantageous for some purposes that a nucleotide sequence be in purified form. The term "purified" in reference to nucleic acid does not require absolute purity (such as a homogeneous preparation).

5 Instead, it represents an indication that the sequence is relatively more pure than in the natural environment (compared to the natural level this level should be at least 2-5 fold greater, e.g., in terms of mg/mL). Individual clones isolated from a cDNA library may be purified to  
10 electrophoretic homogeneity. The claimed DNA molecules obtained from these clones could be obtained directly from total DNA or from total RNA. The cDNA clones are not naturally occurring, but rather are preferably obtained via manipulation of a partially purified naturally occurring  
15 substance (messenger RNA). The construction of a cDNA library from mRNA involves the creation of a synthetic substance (cDNA) and pure individual cDNA clones can be isolated from the synthetic library by clonal selection of the cells carrying the cDNA library. Thus, the process  
20 which includes the construction of a cDNA library from mRNA and isolation of distinct cDNA clones yields an approximately  $10^6$ -fold purification of the native message. Thus, purification of at least one order of magnitude, preferably two or three orders, and more preferably four or  
25 five orders of magnitude is expressly contemplated.

By a "kinase polypeptide" is meant 32 (preferably 40, more preferably 45, most preferably 55) or more contiguous amino acids set forth in the amino acid sequence of SEQ ID NO:5, SEQ ID NO:6, or SEQ ID NO:7, or the corresponding  
30 full-length amino acid sequence; 250 (preferably 255, more preferably 260, most preferably 270) or more contiguous amino acids set forth in the amino acid sequence SEQ ID NO:13, SEQ ID NO:14, SEQ ID NO:15, or SEQ ID NO:105, or the

corresponding full-length amino acid sequence; 27  
(preferably 30, more preferably 40, most preferably 45) or  
more contiguous amino acids set forth in the amino acid  
sequence SEQ ID NO:18; 16 (preferably 20, more preferably  
5 25, most preferably 35) or more contiguous amino acids set  
forth in the amino acid sequence SEQ ID NO:22, SEQ ID NO:23,  
SEQ ID NO:24, SEQ ID NO:29, SEQ ID NO:31, or SEQ ID NO:103  
or the corresponding full-length amino acid sequence; 6  
(preferably 10, more preferably 15, most preferably 25) or  
10 more contiguous amino acids set forth in the amino acid  
sequence of SEQ ID NO:97 or SEQ ID NO:99, 22 (preferably 30,  
more preferably 35, most preferably 45) or more contiguous  
amino acids set forth in the amino acid sequence of SEQ ID  
NO:101, or the corresponding full-length amino acid  
15 sequence; 78 (preferably 80, more preferably 85, most  
preferably 90) or more contiguous amino acids set forth in  
the amino acid sequence SEQ ID NO:107 or functional  
derivatives thereof as described herein. For sequences for  
which the full-length sequence is not given, the remaining  
20 sequences can be determined using methods well-known to  
those in the art and are intended to be included in the  
invention. In certain aspects, polypeptides of 100, 200,  
300 or more amino acids are preferred. The kinase  
polypeptide can be encoded by a full-length nucleic acid  
25 sequence or any portion of the full-length nucleic acid  
sequence, so long as a functional activity of the  
polypeptide is retained, not to include fragments containing  
only amino acids 1-22 of SEQ ID NO:13 or only amino acids 1-  
33 of SEQ ID NO:107.

30 The amino acid sequence will be substantially similar  
to the sequence shown in SEQ ID NO:5, SEQ ID NO:6, SEQ ID  
NO:7, SEQ ID NO:13, SEQ ID NO:14, SEQ ID NO:15, SEQ ID  
NO:18, SEQ ID NO:22, SEQ ID NO:23, SEQ ID NO:24, SEQ ID

NO:29, SEQ ID NO:31, SEQ ID NO:97, SEQ ID NO:99, SEQ ID  
NO:100, SEQ ID NO:103, SEQ ID NO:105, or SEQ ID NO:107, or  
the corresponding full-length amino acid sequence, or  
fragments thereof, not to include fragments consisting only  
5 of the amino acid sequences 1-22 of SEQ ID NO:13 or 1-33 of  
SEQ ID NO:107. A sequence that is substantially similar to  
the sequence of SEQ ID NO:5, SEQ ID NO:6, SEQ ID NO:7, SEQ  
ID NO:13, SEQ ID NO:14, SEQ ID NO:15, SEQ ID NO:18, SEQ ID  
NO:22, SEQ ID NO:23, SEQ ID NO:24, SEQ ID NO:29, SEQ ID  
10 NO:31, SEQ ID NO:97, SEQ ID NO:99, SEQ ID NO:101, SEQ ID  
NO:103, SEQ ID NO:105, or SEQ ID NO:107 will preferably have  
at least 90% identity (more preferably at least 95% and most  
preferably 99-100%) to the sequence of SEQ ID NO:5, SEQ ID  
NO:6, SEQ ID NO:7, SEQ ID NO:13, SEQ ID NO:14, SEQ ID NO:15,  
15 SEQ ID NO:18, SEQ ID NO:22, SEQ ID NO:23, SEQ ID NO:24, SEQ  
ID NO:29, SEQ ID NO:31, SEQ ID NO:97, SEQ ID NO:99, SEQ ID  
NO:101, SEQ ID NO:103, SEQ ID NO:105, or SEQ ID NO:107.

By "identity" is meant a property of sequences that  
measures their similarity or relationship. Identity is  
20 measured by dividing the number of identical residues by the  
total number of residues and gaps and multiplying the  
product by 100. "Gaps" are spaces in an alignment that are  
the result of additions or deletions of amino acids. Thus,  
two copies of exactly the same sequence have 100% identity,  
25 but sequences that are less highly conserved, and have  
deletions, additions, or replacements, may have a lower  
degree of identity. Those skilled in the art will recognize  
that several computer programs are available for determining  
sequence identity using standard parameters, for example  
30 Blast (Altschul, et al. (1997) Nucleic Acids Res. 25:3389-  
3402), Blast2 (Altschul, et al. (1990) J. mol. biol.  
215:403-410), and Smith-Waterman (Smith, et al. (1981) J.  
Mol. Biol. 147:195-197).

In preferred embodiments, the invention features isolated, enriched, or purified nucleic acid molecules encoding a kinase polypeptide comprising a nucleotide sequence that: (a) encodes a polypeptide having the amino acid sequence set forth in SEQ ID NO:5, SEQ ID NO:6, SEQ ID NO:7, SEQ ID NO:13, SEQ ID NO:14, SEQ ID NO:15, SEQ ID NO:18, SEQ ID NO:22, SEQ ID NO:23, SEQ ID NO:24, SEQ ID NO:29, SEQ ID NO:31, SEQ ID NO:97, SEQ ID NO:99, SEQ ID NO:101, SEQ ID NO:103, SEQ ID NO:105, or SEQ ID NO:107; (b) is the complement of the nucleotide sequence of (a); (c) hybridizes under highly stringent conditions to the nucleotide molecule of (a) and encodes a naturally occurring kinase polypeptide; (d) encodes a kinase polypeptide having the amino acid sequence of SEQ ID NO:5, SEQ ID NO:6, SEQ ID NO:7, SEQ ID NO:13, SEQ ID NO:14, SEQ ID NO:15, SEQ ID NO:18, SEQ ID NO:22, SEQ ID NO:23, SEQ ID NO:24, SEQ ID NO:29, SEQ ID NO:31, SEQ ID NO:97, SEQ ID NO:99, SEQ ID NO:103, SEQ ID NO:105, or SEQ ID NO:107, except that it lacks one or more, but not all, of the following segments of amino acid residues: 1-21, 22-274, or 275-416 of SEQ ID NO:5, 1-31, 32-308, 309-489 or 490-516 of SEQ ID NO:6, 1-178 or 179-414 of SEQ ID NO:7, 1-22, 23-289, 290-526, 527-640, 641-896, or 897-1239 of SEQ ID NO:13, 1-255, 256-442, 443-626, 627-954, or 955-1297 of SEQ ID NO:14, 1-255, 256-476, 477-680, 681-983, or 984-1326 of SEQ ID NO:15, 1-13, 14-273, 274-346, 347-534, or 535-894 of SEQ ID NO:18, 1-21, 22-277, 278-427, 428-637, 638-751, or 752-898 of SEQ ID NO:22, 1-66, 67-215, 216-425, 426-539, 540-786, or 787-887 of SEQ ID NO:23, 1-25, 26-273, 274-422, 423-632, or 633-748 of SEQ ID NO:24, 1-51, 52-224, 225-393, 394-658, or 659-681 of SEQ ID NO:29, 1-25, 26-281, 284-430, 431-640, 641-754, 755-901, or 902-1001 of SEQ ID NO:31, 1-10, 11-321, or 322-373 of SEQ ID NO:97, 1-57, 58-369, or 370-418 of SEQ ID NO:99, 1-52, 53-173, 174-

307, 308-572, or 573-591 of SEQ ID NO:103, 1-24, 25-289,  
290-397, 398-628, 629-872, or 873-1227 of SEQ ID NO:105, or  
1-33, 34-294, 295-337, 338-472, 473-724, or 725-968 of SEQ  
ID NO:107; (e) is the complement of the nucleotide sequence  
5 of (d); (f) encodes a polypeptide having the amino acid  
sequence set forth in SEQ ID NO:5, SEQ ID NO:6, SEQ ID NO:7,  
SEQ ID NO:13, SEQ ID NO:14, SEQ ID NO:15, SEQ ID NO:18, SEQ  
ID NO:22, SEQ ID NO:23, SEQ ID NO:24, SEQ ID NO:29, SEQ ID  
NO:31; SEQ ID NO:97, SEQ ID NO:99, SEQ ID NO:103, SEQ ID  
10 NO:105, or SEQ ID NO:107 from amino acid residues 1-21, 22-  
274, or 275-416 of SEQ ID NO:5, 1-31, 32-308, 309-489, or  
490-516 of SEQ ID NO:6, 1-178 or 179-414 of SEQ ID NO:7, 23-  
289, 290-526, 527-640, 641-896, or 897-1239 of SEQ ID NO:13,  
1-255, 256-442, 443-626, 627-954, or 955-1297 of SEQ ID  
15 NO:14, 1-255, 256-476, 477-680, 681-983, or 984-1326 of SEQ  
ID NO:15, 1-13, 14-273, 274-346, 347-534, or 535-894 of SEQ  
ID NO:18, 1-21, 22-277, 278-427, 428-637, 638-751, or 752-  
898 of SEQ ID NO:22, 1-66, 67-215, 216-425, 426-539, 540-  
786, or 787-887 of SEQ ID NO:23, 1-25, 26-273, 274-422, 423-  
20 632, or 633-748 of SEQ ID NO:24, 1-51, 52-224, 225-393, 394-  
658, or 659-681 of SEQ ID NO:29, 1-25, 26-281, 282-430, 431-  
640, 641-754, 755-901, or 902-1001 of SEQ ID NO:31, 1-10,  
11-321, or 322-373 of SEQ ID NO:97, 1-57, 58-369, or 370-418  
of SEQ ID NO:99, 1-52, 53-173, 174-307, 308-572, or 573-591  
25 of SEQ ID NO:103, 1-24, 25-289, 290-397, 398-628, 629-872,  
or 873-1227 of SEQ ID NO:105, or 1-33, 34-294, 295-337, 338-  
472, 473-724, or 725-968 of SEQ ID NO:107; (g) is the  
complement of the nucleotide sequence of (f); (h) encodes a  
polypeptide having the amino acid sequence set forth in SEQ  
30 ID NO:5, SEQ ID NO:6, SEQ ID NO:7, SEQ ID NO:13, SEQ ID  
NO:14, SEQ ID NO:15, SEQ ID NO:18, SEQ ID NO:22, SEQ ID  
NO:23, SEQ ID NO:24, SEQ ID NO:29, SEQ ID NO:31, SEQ ID  
NO:97, SEQ ID NO:99, SEQ ID NO:101, SEQ ID NO:103, SEQ ID

NO:105, or SEQ ID NO:107, except that it lacks one or more of the domains selected from the group consisting of a N-terminal domain, a catalytic domain, a C-terminal domain, a coiled-coil structure region, a proline-rich region, a  
5 spacer region, an insert, and a C-terminal tail; or (i) is the complement of the nucleotide sequence of (h).

The term "complement" refers to two nucleotides that can form multiple favorable interactions with one another. For example, adenine is complementary to thymine as they can  
10 form two hydrogen bonds. Similarly, guanine and cytosine are complementary since they can form three hydrogen bonds.

A nucleotide sequence is the complement of another nucleotide sequence if all of the nucleotides of the first sequence are complementary to all of the nucleotides of the  
15 second sequence.

The term "domain" refers to a region of a polypeptide which contains a particular function. For instance, N-terminal or C-terminal domains of signal transduction proteins can serve functions including, but not limited to,  
20 binding molecules that localize the signal transduction molecule to different regions of the cell or binding other signaling molecules directly responsible for propagating a particular cellular signal. Some domains can be expressed separately from the rest of the protein and function by  
25 themselves, while others must remain part of the intact protein to retain function. The latter are termed functional regions of proteins and also relate to domains.

The term "N-terminal domain" refers to the extracatalytic region located between the initiator  
30 methionine and the catalytic domain of the protein kinase. The N-terminal domain can be identified following a Smith-Waterman alignment of the protein sequence against the non-redundant protein database to define the N-terminal boundary



of the catalytic domain. Depending on its length, the N-terminal domain may or may not play a regulatory role in kinase function. An example of a protein kinase whose N-terminal domain has been shown to play a regulatory role is PAK65, which contains a CRIB motif used for Cdc42 and rac binding (Burbelo, P.D. et al. (1995) J. Biol. Chem. 270, 29071-290740).

The N-terminal domain spans amino acid residues 1-21 of the sequence set forth in SEQ ID NO:5, amino acid residues 1-31 of the sequence set forth in SEQ ID NO:6, amino acid residues 1-22 of the sequence set forth in SEQ ID NO:13, amino acid residues 1-13 of the sequence set forth in SEQ ID NO:18, amino acid residues 1-21 of the sequence set forth in SEQ ID NO:22, amino acid residues 1-25 of the sequence set forth in SEQ ID NO:24, amino acid residues 1-51 of the sequence set forth in SEQ ID NO:29, amino acid residues 1-25 of the sequence set forth in SEQ ID NO:31, amino acid residues 1-57 of the sequence set forth in SEQ ID NO:99, amino acid residues 1-52 of the sequence set forth in SEQ ID NO:103, amino acid residues 1-24 of the sequence set forth in SEQ ID NO:105, or amino acid residues 1-33 of the sequence set forth in SEQ ID NO:107.

The term "catalytic domain" refers to a region of the protein kinase that is typically 25-300 amino acids long and is responsible for carrying out the phosphate transfer reaction from a high-energy phosphate donor molecule such as ATP or GTP to itself (autophosphorylation) or to other proteins (exogenous phosphorylation). The catalytic domain of protein kinases is made up of 12 subdomains that contain highly conserved amino acid residues, and are responsible for proper polypeptide folding and for catalysis. The catalytic domain can be identified following a Smith-

Waterman alignment of the protein sequence against the non-redundant protein database.

5 The catalytic domain spans amino acid residues 22-274  
of the sequence set forth in SEQ ID NO:5, residues 32-308 of  
the sequence set forth in SEQ ID NO:6, residues 1-178 of the  
sequence set forth in SEQ ID NO:7, residues 23-289 of the  
sequence set forth in SEQ ID NO:13, residues 1-255 of the  
sequence set forth in SEQ ID NO:14, residues 1-255 of the  
sequence set forth in SEQ ID NO:15, residues 14-273 of the  
10 sequence set forth in SEQ ID NO:18, residues 22-277 of the  
sequence set forth in SEQ ID NO:22, residues 1-66 of the  
sequence set forth in SEQ ID NO:23, residues 26-273 of the  
sequence set forth in SEQ ID NO:24, residues 394-658 of the  
sequence set forth in SEQ ID NO:29, residues 26-281 of the  
15 sequence set forth in SEQ ID NO:31, residues 1-278 of the  
sequence set forth in SEQ ID NO:97, residues 58-369 of the  
sequence set forth in SEQ ID NO:99, residues 1-103 of the  
sequence set forth in SEQ ID NO:101, residues 308-572 of the  
sequence set forth in SEQ ID NO:103, residues 25-289 of the  
20 sequence set forth in SEQ ID NO:105, or residues 34-294 of  
the sequence set forth in SEQ ID NO:107.

The term "catalytic activity", as used herein, defines  
the rate at which a kinase catalytic domain phosphorylates a  
substrate. Catalytic activity can be measured, for example,  
25 by determining the amount of a substrate converted to a  
phosphorylated product as a function of time. Catalytic  
activity can be measured by methods of the invention by  
holding time constant and determining the concentration of a  
phosphorylated substrate after a fixed period of time.  
30 Phosphorylation of a substrate occurs at the active-site of  
a protein kinase. The active-site is normally a cavity in  
which the substrate binds to the protein kinase and is  
phosphorylated.

The term "substrate" as used herein refers to a molecule phosphorylated by a kinase of the invention. Kinases phosphorylate substrates on serine/threonine or tyrosine amino acids. The molecule may be another protein or a polypeptide.

The term "C-terminal domain" refers to the region located between the catalytic domain or the last (located closest to the C-terminus) functional domain and the carboxy-terminal amino acid residue of the protein kinase. By "functional" domain is meant any region of the polypeptide that may play a regulatory or catalytic role as predicted from amino acid sequence homology to other proteins or by the presence of amino acid sequences that may give rise to specific structural conformations (i.e. coiled-coils). The C-terminal domain can be identified by using a Smith-Waterman alignment of the protein sequence against the non-redundant protein database to define the C-terminal boundary of the catalytic domain or of any functional C-terminal extracatalytic domain. Depending on its length and amino acid composition, the C-terminal domain may or may not play a regulatory role in kinase function. An example of a protein kinase whose C-terminal domain may play a regulatory role is PAK3 which contains a heterotrimeric G<sub>b</sub> subunit-binding site near its C-terminus (Leeuw, T. et al (1998) Nature, 391, 191-195).

The C-terminal domain spans amino acid residues 275-416 of the sequence set forth in SEQ ID NO:5, residues 309-489 of the sequence set forth in SEQ ID NO:6, residues 179-414 of the sequence set forth in SEQ ID NO:7, residues 897-1239 of the sequence set forth in SEQ ID NO:13, residues 955-1297 of the sequence set forth in SEQ ID NO:14, residues 984-1326 of the sequence set forth in SEQ ID NO:15, residues 535-894 of the sequence set forth in SEQ ID NO:18, residues 752-898

of the sequence set forth in SEQ ID NO:22, residues 279-330 of the sequence set forth in SEQ ID NO:97, residues 370-418 of the sequence set forth in SEQ ID NO:99, or residues 873-1227 of the sequence set forth in SEQ ID NO:105.

5           The term "signal transduction pathway" refers to the molecules that propagate an extracellular signal through the cell membrane to become an intracellular signal. This signal can then stimulate a cellular response. The polypeptide molecules involved in signal transduction  
10       processes are typically receptor and non-receptor protein tyrosine kinases, receptor and non-receptor protein phosphatases, SRC homology 2 and 3 domains, phosphotyrosine binding proteins (SRC homology 2 (SH2) and phosphotyrosine binding (PTB and PH) domain containing proteins), proline-  
15       rich binding proteins (SH3 domain containing proteins), nucleotide exchange factors, and transcription factors.

          The term "coiled-coil structure region" as used herein, refers to a polypeptide sequence that has a high probability of adopting a coiled-coil structure as predicted by computer  
20       algorithms such as COILS (Lupas, A. (1996) Meth. Enzymology 266:513-525). Coiled-coils are formed by two or three amphipathic  $\alpha$ -helices in parallel. Coiled-coils can bind to coiled-coil domains of other polypeptides resulting in homo- or heterodimers (Lupas, A. (1991) Science 252:1162-1164).  
25       Coiled-coil-dependent oligomerization has been shown to be necessary for protein function including catalytic activity of serine/threonine kinases (Roe, J. et al. (1997) J. Biol. Chem. 272:5838-5845).

          The coiled-coil structure region spans amino acid  
30       residues 290-526 of the sequence set forth in SEQ ID NO:13, residues 256-442 of the sequence set forth in SEQ ID NO:14, residues 256-476 of the sequence set forth in SEQ ID NO:15, residues 428-637 of the sequence set forth in SEQ ID NO:22,

residues 216-425 or 540-786 of the sequence set forth in SEQ ID NO:23, residues 423-632 of the sequence set forth in SEQ ID NO:24, residues 431-640 or 755-901 of the sequence set forth in SEQ ID NO:31, residues 291-398 or 629-668 of the sequence set forth in SEQ ID NO:105, or residues 473-724 or 725-968 of the sequence set forth in SEQ ID NO:107.

The term "proline-rich region" as used herein, refers to a region of a protein kinase whose proline content over a given amino acid length is higher than the average content of this amino acid found in proteins(i.e., >10%). Proline-rich regions are easily discernable by visual inspection of amino acid sequences and quantitated by standard computer sequence analysis programs such as the DNASTar program EditSeq. Proline-rich regions have been demonstrated to participate in regulatory protein -protein interactions. Among these interactions, those that are most relevant to this invention involve the "PxxP" proline rich motif found in certain protein kinases (i.e., human PAK1) and the SH3 domain of the adaptor molecule Nck (Galisteo, M.L. et al. (1996) J. Biol. Chem. 271:20997-21000). Other regulatory interactions involving "PxxP" proline-rich motifs include the WW domain (Sudol, M. (1996) Prog. Biochys. Mol. Bio. 65:113-132).

The proline-rich region spans amino acid residues 527-640 of the sequence set forth in SEQ ID NO:13, residues 443-626 of the sequence set forth in SEQ ID NO:14, residues 477-680 of the sequence set forth in SEQ ID NO:15, residues 347-534 of the sequence set forth in SEQ ID NO:18, residues 398-628 of the sequence set forth in SEQ ID NO:105, or residues 338-472 of the sequence set forth in SEQ ID NO:107.

The term "spacer region" as used herein, refers to a region of the protein kinase located between predicted functional domains. The spacer region has no detectable

homology to any amino acid sequence in the database, and can be identified by using a Smith-Waterman alignment of the protein sequence against the non-redundant protein database to define the C- and N-terminal boundaries of the flanking functional domains. Spacer regions may or may not play a fundamental role in protein kinase function. Precedence for the regulatory role of spacer regions in kinase function is provided by the role of the src kinase spacer in inter-domain interactions (Xu, W. et al. (1997) Nature 385:595-602).

The spacer region spans amino acid residues 641-896 of the sequence set forth in SEQ ID NO:13, residues 627-954 of the sequence set forth in SEQ ID NO:14, residues 681-983 of the sequence set forth in SEQ ID NO:15, residues 274-346 of the sequence set forth in SEQ ID NO:18, residues 278-427 or 638-751 of the sequence set forth in SEQ ID NO:22, residues 67-215 or 426-539 of the sequence set forth in SEQ ID NO:23, residues 274-422 or 633-748 of the sequence set forth in SEQ ID NO:24, residues 225-393 of the sequence set forth in SEQ ID NO:29, residues 282-430 or 641-754 of the sequence set forth in SEQ ID NO:31, residues 174-307 of the sequence set forth in SEQ ID NO:103, residues 669-872 of the sequence set forth in SEQ ID NO:105, or residues 295-337 of the sequence set forth in SEQ ID NO:107.

The term "insert" as used herein refers to a portion of a protein kinase that is absent from a close homolog. Inserts may or may not be the product of alternative splicing of exons. Inserts can be identified by using a Smith-Waterman sequence alignment of the protein sequence against the non-redundant protein database, or by means of a multiple sequence alignment of homologous sequences using the DNASTar program Megalign. Inserts may play a functional role by presenting a new interface for protein-protein

interactions, or by interfering with such interactions.

Inserts span amino acid residues 52-224 of the sequence set forth in SEQ ID NO:29 or residues 53-173 of the sequence set forth in SEQ ID NO:103.

5           The term "C-terminal tail" as used herein, refers to a C-terminal domain of a protein kinase, that by homology extends or protrudes past the C-terminal amino acid of its closest homolog. C-terminal tails can be identified by using a Smith-Waterman sequence alignment of the protein  
10           sequence against the non-redundant protein database, or by means of a multiple sequence alignment of homologous sequences using the DNASTar program Megalign. Depending on its length, a C-terminal tail may or may not play a regulatory role in kinase function.

15           The C-terminal tail spans amino acid residues 490-516 of the sequence set forth in SEQ ID NO:6, residues 787-887 of the sequence set forth in SEQ ID NO:23, residues 659-681 of the sequence set forth in SEQ ID NO:29, residues 994-1093 of the sequence set forth in SEQ ID NO:31, or residues 573-  
20           591 of the sequence set forth in SEQ ID NO:103.

          Various low or high stringency hybridization conditions may be used depending upon the specificity and selectivity desired. These conditions are well-known to those skilled in the art. Under stringent hybridization conditions only  
25           highly complementary nucleic acid sequences hybridize. Preferably, such conditions prevent hybridization of nucleic acids having more than 1 or 2 mismatches out of 20 contiguous nucleotides, more preferably, such conditions prevent hybridization of nucleic acids having more than 1 or  
30           2 mismatches out of 50 contiguous nucleotides, most preferably, such conditions prevent hybridization of nucleic acids having more than 1 or 2 mismatches out of 100 contiguous nucleotides. In some instances, the conditions

may prevent hybridization of nucleic acids having more than 5 mismatches in the full-length sequence.

By stringent hybridization assay conditions is meant hybridization assay conditions at least as stringent as the following: hybridization in 50% formamide, 5X SSC, 50 mM NaH<sub>2</sub>PO<sub>4</sub>, pH 6.8, 0.5% SDS, 0.1 mg/mL sonicated salmon sperm DNA, and 5X Denhart solution at 42 °C overnight; washing with 2X SSC, 0.1% SDS at 45 °C; and washing with 0.2X SSC, 0.1% SDS at 45 °C. Under some of the most stringent hybridization assay conditions, the second wash can be done with 0.1X SSC at a temperature up to 70 °C (Berger et al. (1987) Guide to Molecular Cloning Techniques pg 421, hereby incorporated by reference herein including any figures, tables, or drawings.). However, other applications may require the use of conditions falling between these sets of conditions. Methods of determining the conditions required to achieve desired hybridizations are well-known to those with ordinary skill in the art, and are based on several factors, including but not limited to, the sequences to be hybridized and the samples to be tested.

In other preferred embodiments, the invention features isolated, enriched, or purified nucleic acid molecules encoding kinase polypeptides, further comprising a vector or promoter effective to initiate transcription in a host cell.

The invention also features recombinant nucleic acid, preferably in a cell or an organism. The recombinant nucleic acid may contain a sequence set forth in SEQ ID NO:1, SEQ ID NO:2, SEQ ID NO:3, SEQ ID NO:9, SEQ ID NO:10, SEQ ID NO:11, SEQ ID NO:17, SEQ ID NO:19, SEQ ID NO:20, SEQ ID NO:21, SEQ ID NO:27, SEQ ID NO:96, SEQ ID NO:98, SEQ ID NO:100, SEQ ID NO:102, SEQ ID NO:104, or SEQ ID NO:106, or a functional derivative thereof and a vector or a promoter effective to initiate transcription in a host cell. The



recombinant nucleic acid can alternatively contain a transcriptional initiation region functional in a cell, a sequence complementary to an RNA sequence encoding a kinase polypeptide and a transcriptional termination region functional in a cell. Specific vectors and host cell combinations are discussed herein.

The term "vector" relates to a single or double-stranded circular nucleic acid molecule that can be transfected into cells and replicated within or independently of a cell genome. A circular double-stranded nucleic acid molecule can be cut and thereby linearized upon treatment with restriction enzymes. An assortment of nucleic acid vectors, restriction enzymes, and the knowledge of the nucleotide sequences cut by restriction enzymes are readily available to those skilled in the art. A nucleic acid molecule encoding a kinase can be inserted into a vector by cutting the vector with restriction enzymes and ligating the two pieces together.

The term "transfecting" defines a number of methods to insert a nucleic acid vector or other nucleic acid molecules into a cellular organism. These methods involve a variety of techniques, such as treating the cells with high concentrations of salt, an electric field, detergent, or DMSO to render the outer membrane or wall of the cells permeable to nucleic acid molecules of interest or use of various viral transduction strategies.

The term "promoter" as used herein, refers to nucleic acid sequence needed for gene sequence expression. Promoter regions vary from organism to organism, but are well known to persons skilled in the art for different organisms. For example, in prokaryotes, the promoter region contains both the promoter (which directs the initiation of RNA transcription) as well as the DNA sequences which, when

transcribed into RNA, will signal synthesis initiation. Such regions will normally include those 5'-non-coding sequences involved with initiation of transcription and translation, such as the TATA box, capping sequence, CAAT sequence, and the like.

In preferred embodiments, the isolated nucleic acid comprises, consists essentially of, or consists of a nucleic acid sequence set forth in SEQ ID NO:1, SEQ ID NO:2, SEQ ID NO:3, SEQ ID NO:9, SEQ ID NO:10, SEQ ID NO:11, SEQ ID NO:17, SEQ ID NO:19, SEQ ID NO:20, SEQ ID NO:21, SEQ ID NO:27, SEQ ID NO:96, SEQ ID NO:98, SEQ ID NO:100, SEQ ID NO:102, SEQ ID NO:104, or SEQ ID NO:106, or the corresponding full-length sequence, encodes the amino acid sequence of SEQ ID NO:5, SEQ ID NO:6, SEQ ID NO:7, SEQ ID NO:13, SEQ ID NO:14, SEQ ID NO:15, SEQ ID NO:18, SEQ ID NO:22, SEQ ID NO:23, SEQ ID NO:24, SEQ ID NO:29, SEQ ID NO:31, SEQ ID NO:97, SEQ ID NO:99, SEQ ID NO:101, SEQ ID NO:103, SEQ ID NO:105, or SEQ ID NO:107, or the corresponding full-length amino acid sequence, a functional derivative thereof, or at least 40, 45, 50, 60, 100, 200, or 300 contiguous amino acids of SEQ ID NO:5, SEQ ID NO:6, or SEQ ID NO:7, or of the corresponding full-length amino acid sequence; at least 250, 255, 275, 300, or 400 contiguous amino acids of SEQ ID NO:13, SEQ ID NO:14, SEQ ID NO:15, or of the corresponding full-length amino acid sequence; at least 27, 30, 35, 40, 50, 100, 200, or 300 contiguous amino acids of SEQ ID NO:18; at least 16, 25, 35, 50, 100, 200, or 300 contiguous amino acids of SEQ ID NO:22, SEQ ID NO:23, SEQ ID NO:24, SEQ ID NO:29, SEQ ID NO:31, or SEQ ID NO:103, or of the corresponding full-length amino acid sequence; 6 (preferably 10, more preferably 15, most preferably 25) or more contiguous amino acids set forth in the amino acid sequence of SEQ ID NO:97 or SEQ ID NO:99, or the corresponding full-

length amino acid sequence; 22 (preferably 30, more preferably 35, most preferably 45) or more contiguous amino acids set forth in the amino acid sequence of SEQ ID NO:101, or the corresponding full-length amino acid sequence; or at least 80, 85, 90, 100, 200, or 300 contiguous amino acids of SEQ ID NO:107, or functional derivatives thereof. The kinase polypeptides, selected from the group consisting of STLK2, STLK3, STLK4, STLK5, STLK6, STLK7, ZC1, ZC2, ZC3, ZC4, KHS2, SULU1, SULU3, GEK2, PAK4, and PAK5, comprise, consist essentially of, or consist of at least at least 40, 45, 50, 60, 100, 200, or 300 contiguous amino acids of SEQ ID NO:5, SEQ ID NO:6, or SEQ ID NO:7; at least 250, 255, 275, 300, or 400 contiguous amino acids of SEQ ID NO:13, SEQ ID NO:14, SEQ ID NO:15, or SEQ ID NO:105; at least 27, 30, 35, 40, 50, 100, 200, or 300 contiguous amino acids of SEQ ID NO:18; at least 35, 40, 45, 50, 100, 200, or 300 contiguous amino acids of SEQ ID NO:22, SEQ ID NO:23, SEQ ID NO:24, SEQ ID NO:29, SEQ ID NO:31 or SEQ ID NO:103; 6 (preferably 10, more preferably 15, most preferably 25) or more contiguous amino acids set forth in the amino acid sequence of SEQ ID NO:97 or SEQ ID NO:99; 22 (preferably 30, more preferably 35, most preferably 45) or more contiguous amino acids set forth in the amino acid sequence of SEQ ID NO:101; or at least 80, 85, 90, 100, 200, or 300 contiguous amino acids of SEQ ID NO:107, or the corresponding full-length sequences or derivatives thereof. The nucleic acid may be isolated from a natural source by cDNA cloning or by subtractive hybridization. The natural source may be mammalian, preferably human, blood, semen, or tissue, and the nucleic acid may be synthesized by the triester method or by using an automated DNA synthesizer.

The term "mammal" refers preferably to such organisms as mice, rats, rabbits, guinea pigs, sheep, and goats, more

preferably to cats, dogs, monkeys, and apes, and most preferably to humans.

In yet other preferred embodiments, the nucleic acid is a conserved or unique region, for example those useful for:  
5 the design of hybridization probes to facilitate identification and cloning of additional polypeptides, the design of PCR probes to facilitate cloning of additional polypeptides, obtaining antibodies to polypeptide regions, and designing antisense oligonucleotides.

10 By "conserved nucleic acid regions", are meant regions present on two or more nucleic acids encoding a kinase polypeptide, to which a particular nucleic acid sequence can hybridize under lower stringency conditions. Examples of lower stringency conditions suitable for screening for  
15 nucleic acid encoding kinase polypeptides are provided in Abe, et al. (J. Biol. Chem. 19:13361-13368, 1992), hereby incorporated by reference herein in its entirety, including any drawings, figures, or tables. Preferably, conserved regions differ by no more than 5 out of 20 nucleotides, even  
20 more preferably 2 out of 20 nucleotides or most preferably 1 out of 20 nucleotides.

By "unique nucleic acid region" is meant a sequence present in a nucleic acid coding for a kinase polypeptide that is not present in a sequence coding for any other  
25 naturally occurring polypeptide. Such regions preferably encode 32 (preferably 40, more preferably 45, most preferably 55) or more contiguous amino acids set forth in the amino acid sequence of SEQ ID NO:5, SEQ ID NO:6, or SEQ ID NO:7, or the corresponding full-length amino acid  
30 sequence; 250 (preferably 255, more preferably 260, most preferably 270) or more contiguous amino acids set forth in the amino acid sequence SEQ ID NO:13, SEQ ID NO:14, or SEQ ID NO:15, or SEQ ID NO:105, or the corresponding full-length

amino acid sequence; 27 (preferably 30, more preferably 40, most preferably 45) or more contiguous amino acids set forth in the amino acid sequence SEQ ID NO:18; 16 (preferably 20, more preferably 25, most preferably 35) or more contiguous amino acids set forth in the amino acid sequence SEQ ID NO:22, SEQ ID NO:23, SEQ ID NO:24, SEQ ID NO:29, SEQ ID NO:31, or SEQ ID NO:103, or the corresponding full-length amino acid sequence; 6 (preferably 10, more preferably 15, most preferably 25) or more contiguous amino acids set forth in the amino acid sequence of SEQ ID NO:97 or SEQ ID NO:99, 22 (preferably 30, more preferably 35, most preferably 45) or more contiguous amino acids set forth in the amino acid sequence of SEQ ID NO:101, or the corresponding full-length amino acid sequence; or 78 (preferably 80, more preferably 85, most preferably 90) or more contiguous amino acids set forth in the amino acid sequence SEQ ID NO:107, or functional derivatives thereof. In particular, a unique nucleic acid region is preferably of mammalian origin.

A second aspect of the invention features a nucleic acid probe for the detection of nucleic acid encoding a kinase polypeptide in a sample, wherein said polypeptide is selected from the group consisting of STLK2, STLK3, STLK4, STLK5, STLK6, STLK7, ZC1, ZC2, ZC3, ZC4, KHS2, SULU1, SULU3, GEK2, PAK4, and PAK5. Preferably, the nucleic acid probe encodes a kinase polypeptide that is a fragment of the protein encoded by the amino acid sequence set forth in SEQ ID NO:5, SEQ ID NO:6, SEQ ID NO:7, SEQ ID NO:13, SEQ ID NO:14, SEQ ID NO:15, SEQ ID NO:18, SEQ ID NO:22, SEQ ID NO:23, SEQ ID NO:24, SEQ ID NO:29, SEQ ID NO:31, SEQ ID NO:97, SEQ ID NO:99, SEQ ID NO:101, SEQ ID NO:103, SEQ ID NO:105, or SEQ ID NO:107, or the corresponding full-length amino acid sequences, not to include fragments consisting only of amino acids 1-22 of SEQ ID NO:13 or amino acids 1-33

of SEQ ID NO:107. The nucleic acid probe contains a nucleotide base sequence that will hybridize to a sequence set forth in SEQ ID NO:1, SEQ ID NO:2, SEQ ID NO:3, SEQ ID NO:9, SEQ ID NO:10, SEQ ID NO:11, SEQ ID NO:17, SEQ ID NO:19, SEQ ID NO:20, SEQ ID NO:21, SEQ ID NO:27, SEQ ID NO:96, SEQ ID NO:98, SEQ ID NO:100, SEQ ID NO:102, SEQ ID NO:104, or SEQ ID NO:106, or the corresponding full-length sequence, or a functional derivative thereof.

In preferred embodiments, the nucleic acid probe hybridizes to nucleic acid encoding at least 6, 12, 75, 90, 105, 120, 150, 200, 250, 300 or 350 contiguous amino acids of the sequence set forth in SEQ ID NO:5, SEQ ID NO:6, SEQ ID NO:7, SEQ ID NO:13, SEQ ID NO:14, SEQ ID NO:15, SEQ ID NO:18, SEQ ID NO:22, SEQ ID NO:23, SEQ ID NO:24, SEQ ID NO:29, SEQ ID NO:31, SEQ ID NO:97, SEQ ID NO:99, SEQ ID NO:101, SEQ ID NO:103, SEQ ID NO:105, or SEQ ID NO:107, or the corresponding full-length amino acid sequence, or functional derivatives thereof.

Methods for using the probes include detecting the presence or amount of kinase RNA in a sample by contacting the sample with a nucleic acid probe under conditions such that hybridization occurs and detecting the presence or amount of the probe bound to kinase RNA. The nucleic acid duplex formed between the probe and a nucleic acid sequence coding for a kinase polypeptide may be used in the identification of the sequence of the nucleic acid detected (Nelson et al., in *Nonisotopic DNA Probe Techniques*, Academic Press, San Diego, Kricka, ed., p. 275, 1992, hereby incorporated by reference herein in its entirety, including any drawings, figures, or tables). Kits for performing such methods may be constructed to include a container means having disposed therein a nucleic acid probe.

In a third aspect, the invention describes a recombinant cell or tissue comprising a nucleic acid molecule encoding a kinase polypeptide selected from the group consisting of STLK2, STLK3, STLK4, STLK5, STLK6, 5 STLK7, ZC1, ZC2, ZC3, ZC4, KHS2, SULU1, SULU3, GEK2, PAK4, and PAK5. In such cells, the nucleic acid may be under the control of the genomic regulatory elements, or may be under the control of exogenous regulatory elements including an exogenous promoter. By "exogenous" it is meant a promoter 10 that is not normally coupled *in vivo* transcriptionally to the coding sequence for the kinase polypeptides.

The polypeptide is preferably a fragment of the protein encoded by the amino acid sequence set forth in SEQ ID NO:5, SEQ ID NO:6, SEQ ID NO:7, SEQ ID NO:13, SEQ ID NO:14, SEQ ID 15 NO:15, SEQ ID NO:18, SEQ ID NO:22, SEQ ID NO:23, SEQ ID NO:24, SEQ ID NO:29, SEQ ID NO:31, SEQ ID NO:97, SEQ ID NO:99, SEQ ID NO:101, SEQ ID NO:103, SEQ ID NO:105, or SEQ ID NO:107, or the corresponding full-length amino acid sequence, not to include fragments consisting only of amino 20 acids 1-22 of SEQ ID NO:13 or amino acids 1-33 of SEQ ID NO:107. By "fragment," is meant an amino acid sequence present in a kinase polypeptide. Preferably, such a sequence comprises at least 32, 45, 50, 60, 100, 200, or 300 contiguous amino acids of SEQ ID NO:5, SEQ ID NO:6, or SEQ 25 ID NO:7, or of the corresponding full-length amino acid sequence; at least 250, 255, 275, 300, or 400 contiguous amino acids of SEQ ID NO:13, SEQ ID NO:14, SEQ ID NO:15, OR SEQ ID NO:105, or of the corresponding full-length amino acid sequence; at least 27, 30, 35, 40, 50, 100, 200, or 300 30 contiguous amino acids of SEQ ID NO:18; at least 16, 25, 35, 50, 100, 200, or 300 contiguous amino acids of SEQ ID NO:22, SEQ ID NO:23, SEQ ID NO:24, SEQ ID NO:29, SEQ ID NO:31 or SEQ ID NO:103, or of the corresponding full-length amino

acid sequence; 6 (preferably 10, more preferably 15, most preferably 25) or more contiguous amino acids set forth in the amino acid sequence of SEQ ID NO:97 or SEQ ID NO:99, 22 (preferably 30, more preferably 35, most preferably 45) or  
5 more contiguous amino acids set forth in the amino acid sequence of SEQ ID NO:101; at least 78, 85, 90, 100, 200, or 300 contiguous amino acids of SEQ ID NO:107, or the corresponding full-length amino acid sequence; or a functional derivative thereof.

10 In a fourth aspect, the invention features an isolated, enriched, or purified kinase polypeptide selected from the group consisting of STLK2, STLK3, STLK4, STLK5, STLK6, STLK7, ZC1, ZC2, ZC3, ZC4, KHS2, SULU1, SULU3, GEK2, PAK4, and PAK5.

15 By "isolated" in reference to a polypeptide is meant a polymer of amino acids (2 or more amino acids) conjugated to each other, including polypeptides that are isolated from a natural source or that are synthesized. The isolated polypeptides of the present invention are unique in the  
20 sense that they are not found in a pure or separated state in nature. Use of the term "isolated" indicates that a naturally occurring sequence has been removed from its normal cellular environment. Thus, the sequence may be in a cell-free solution or placed in a different cellular  
25 environment. The term does not imply that the sequence is the only amino acid chain present, but that it is essentially free (about 90 - 95% pure at least) of non-amino acid material naturally associated with it.

30 By the use of the term "enriched" in reference to a polypeptide is meant that the specific amino acid sequence constitutes a significantly higher fraction (2 - 5 fold) of the total amino acid sequences present in the cells or solution of interest than in normal or diseased cells or in



the cells from which the sequence was taken. This could be caused by a person by preferential reduction in the amount of other amino acid sequences present, or by a preferential increase in the amount of the specific amino acid sequence of interest, or by a combination of the two. However, it should be noted that enriched does not imply that there are no other amino acid sequences present, just that the relative amount of the sequence of interest has been significantly increased. The term significant here is used to indicate that the level of increase is useful to the person making such an increase, and generally means an increase relative to other amino acid sequences of about at least 2-fold, more preferably at least 5- to 10-fold or even more. The term also does not imply that there is no amino acid sequence from other sources. The other source of amino acid sequences may, for example, comprise amino acid sequence encoded by a yeast or bacterial genome, or a cloning vector such as pUC19. The term is meant to cover only those situations in which man has intervened to increase the proportion of the desired amino acid sequence.

It is also advantageous for some purposes that an amino acid sequence be in purified form. The term "purified" in reference to a polypeptide does not require absolute purity (such as a homogeneous preparation); instead, it represents an indication that the sequence is relatively purer than in the natural environment. Compared to the natural level this level should be at least 2-5 fold greater (e.g., in terms of mg/mL). Purification of at least one order of magnitude, preferably two or three orders, and more preferably four or five orders of magnitude is expressly contemplated. The substance is preferably free of contamination at a functionally significant level, for example 90%, 95%, or 99% pure.

In preferred embodiments, the kinase polypeptide is a fragment of the protein encoded by the amino acid sequence set forth in SEQ ID NO:5, SEQ ID NO:6, SEQ ID NO:7, SEQ ID NO:13, SEQ ID NO:14, SEQ ID NO:15, SEQ ID NO:18, SEQ ID NO:22, SEQ ID NO:23, SEQ ID NO:24, SEQ ID NO:29, SEQ ID NO:31, SEQ ID NO:97, SEQ ID NO:99, SEQ ID NO:101, SEQ ID NO:103, SEQ ID NO:105, or SEQ ID NO:107, or the corresponding full-length amino acid sequences, not to include fragments consisting only of amino acids 1-22 of SEQ ID NO:13 or amino acids 1-33 of SEQ ID NO:107. Preferably, the kinase polypeptide contains at least 32, 45, 50, 60, 100, 200, or 300 contiguous amino acids of SEQ ID NO:5, SEQ ID NO:6, or SEQ ID NO:7, or the corresponding full-length amino acid sequence; at least 250, 255, 275, 300, or 400 contiguous amino acids of SEQ ID NO:13, SEQ ID NO:14, SEQ ID NO:15, or SEQ ID NO:105, or the corresponding full-length amino acid sequence; at least 27, 30, 35, 40, 50, 100, 200, or 300 contiguous amino acids of SEQ ID NO:18; at least 16, 25, 35, 50, 100, 200, or 300 contiguous amino acids of SEQ ID NO:22, SEQ ID NO:23, SEQ ID NO:24, SEQ ID NO:29, SEQ ID NO:31, or SEQ ID NO:103, or the corresponding full-length amino acid sequence; 6 (preferably 10, more preferably 15, most preferably 25) or more contiguous amino acids set forth in the amino acid sequence of SEQ ID NO:97 or SEQ ID NO:99, 22 (preferably 30, more preferably 35, most preferably 45) or more contiguous amino acids set forth in the amino acid sequence of SEQ ID NO:101, or the corresponding full-length amino acid sequence; or at least 78, 85, 90, 100, 200, or 300 contiguous amino acids of SEQ ID NO:107, or a functional derivative thereof.

In preferred embodiments, the kinase polypeptide comprises an amino acid sequence having (a) the amino acid sequence set forth in SEQ ID NO:5, SEQ ID NO:6, SEQ ID NO:7,

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SEQ ID NO:13, SEQ ID NO:14, SEQ ID NO:15, SEQ ID NO:18, SEQ ID NO:22, SEQ ID NO:23, SEQ ID NO:24, SEQ ID NO:29, SEQ ID NO:31, SEQ ID NO:97, SEQ ID NO:99, SEQ ID NO:101, SEQ ID NO:103, SEQ ID NO:105, or SEQ ID NO:107; (b) the amino acid sequence set forth in SEQ ID NO:5, SEQ ID NO:6, SEQ ID NO:7, SEQ ID NO:13, SEQ ID NO:14, SEQ ID NO:15, SEQ ID NO:18, SEQ ID NO:22, SEQ ID NO:23, SEQ ID NO:24, SEQ ID NO:29, SEQ ID NO:31, SEQ ID NO:97, SEQ ID NO:99, SEQ ID NO:103, SEQ ID NO:105, or SEQ ID NO:107, except that it lacks one or more, but not all, of the following segments of amino acid residues: 1-21, 22-274, or 275-416 of SEQ ID NO:5, 1-31, 32-308, 309-489 or 490-516 of SEQ ID NO:6, 1-178 or 179-414 of SEQ ID NO:7, 1-22, 23-289, 290-526, 527-640, 641-896, or 897-1239 of SEQ ID NO:13, 1-255, 256-442, 443-626, 627-954, or 955-1297 of SEQ ID NO:14, 1-255, 256-476, 477-680, 681-983, or 984-1326 of SEQ ID NO:15, 1-13, 14-273, 274-346, 347-534, or 535-894 of SEQ ID NO:18, 1-21, 22-277, 278-427, 428-637, 638-751, or 752-898 of SEQ ID NO:22, 1-66, 67-215, 216-425, 426-539, 540-786, or 787-887 of SEQ ID NO:23, 1-25, 26-273, 274-422, 423-632, or 633-748 of SEQ ID NO:24, 1-51, 52-224, 225-393, 394-658, or 659-681 of SEQ ID NO:29, 1-25, 26-281, 282-430, 431-640, 641-754, 755-901, or 902-1001 of SEQ ID NO:31, 1-10, 11-321, or 322-373 of SEQ ID NO:97, 1-57, 58-369, or 370-418 of SEQ ID NO:99, 1-52, 53-173, 174-307, 308-572, or 573-591 of SEQ ID NO:103, 1-24, 25-289, 290-397, 398-628, 629-668, 669-872, or 873-1227 of SEQ ID NO:105, or 1-33, 34-294, 295-337, 338-472, 473-724, or 725-968 of SEQ ID NO:107; (c) the amino acid sequence set forth in SEQ ID NO:5, SEQ ID NO:6, SEQ ID NO:7, SEQ ID NO:13, SEQ ID NO:14, SEQ ID NO:15, SEQ ID NO:18, SEQ ID NO:22, SEQ ID NO:23, SEQ ID NO:24, SEQ ID NO:29, SEQ ID NO:97, SEQ ID NO:99, SEQ ID NO:103, SEQ ID NO:105, or SEQ ID NO:107 from amino acid residues 1-21, 22-274, or 275-416 of

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SEQ ID NO:5, 1-31, 32-308, 309-489, or 490-516 of SEQ ID  
 NO:6, 1-178 or 179-414 of SEQ ID NO:7, 23-289, 290-526, 527-  
 640, 641-896, or 897-1239 of SEQ ID NO:13, 1-255, 256-442,  
 443-626, 627-954, or 955-1297 of SEQ ID NO:14, 1-255, 256-  
 5 476, 477-680, 681-983, or 984-1326 of SEQ ID NO:15, 1-13,  
 14-273, 274-346, 347-534, or 535-894 of SEQ ID NO:18, 1-21,  
 22-277, 278-427, 428-637, 638-751, or 752-898 of SEQ ID  
 NO:22, 1-66, 67-215, 216-425, 426-539, 540-786, or 787-887  
 of SEQ ID NO:23, 1-25, 26-273, 274-422, 423-632, or 633-748  
 10 of SEQ ID NO:24, 1-51, 52-224, 225-393, 394-658, or 659-681  
 of SEQ ID NO:29, 1-25, 26-273, 274-422, 423-632, 633-746,  
 747-993, or 994-1093 of SEQ ID NO:31, 1-10, 11-321, or 322-  
 373 of SEQ ID NO:97, 1-57, 58-369, or 370-418 of SEQ ID  
 NO:99, 1-52, 53-173, 174-307, 308-572, or 573-591 of SEQ ID  
 15 NO:103, 1-24, 25-289, 290-397, 398-628, 629-668, 669-872, or  
 873-1227 of SEQ ID NO:105, or 1-33, 34-294, 295-337, 338-  
 472, 473-724, or 725-968 of SEQ ID NO:107; or (d) the amino  
 acid sequence set forth in SEQ ID NO:5, SEQ ID NO:6, SEQ ID  
 NO:7, SEQ ID NO:13, SEQ ID NO:14, SEQ ID NO:15, SEQ ID  
 20 NO:18, SEQ ID NO:22, SEQ ID NO:23, SEQ ID NO:24, SEQ ID  
 NO:29, SEQ ID NO:31, SEQ ID NO:97, SEQ ID NO:99, SEQ ID  
 NO:101, SEQ ID NO:103, SEQ ID NO:105, or SEQ ID NO:107,  
 except that it lacks one or more, but not all, of the  
 domains selected from the group consisting of a C-terminal  
 25 domain, a catalytic domain, an N-terminal domain, a spacer  
 region, a proline-rich region, a coiled-coil structure  
 region, an insert, and a C-terminal tail.

The polypeptide can be isolated from a natural source  
 by methods well-known in the art. The natural source may be  
 30 mammalian, preferably human, blood, semen, or tissue, and  
 the polypeptide may be synthesized using an automated  
 polypeptide synthesizer. The isolated, enriched, or  
 purified kinase polypeptide is preferably: a STLK2, STLK3,

STLK4, STLK5, STLK6, or STLK7 polypeptide; a ZC1, ZC2, ZC3, or ZC4 polypeptide; a KHS2 polypeptide; a SULU1 or SULU3 polypeptide; a GEK2 polypeptide; or a PAK4 or PAK5 polypeptide.

5           In some embodiments the invention includes a recombinant kinase polypeptide selected from the group consisting of STLK2, STLK3, STLK4, STLK5, STLK6, STLK7, ZC1, ZC2, ZC3, ZC4, KHS2, SULU1, SULU3, GEK2, PAK4, and PAK5. By "recombinant kinase polypeptide" is meant a polypeptide  
10       produced by recombinant DNA techniques such that it is distinct from a naturally occurring polypeptide either in its location (e.g., present in a different cell or tissue than found in nature), purity or structure. Generally, such a recombinant polypeptide will be present in a cell in an  
15       amount different from that normally observed in nature.

          In a fifth aspect, the invention features an antibody (e.g., a monoclonal or polyclonal antibody) having specific binding affinity to a kinase polypeptide or a kinase  
20       polypeptide domain or fragment where the polypeptide is selected from the group consisting of STLK2, STLK3, STLK4, STLK5, STLK6, STLK7, ZC1, ZC2, ZC3, ZC4, KHS2, SULU1, SULU3, GEK2, PAK4, and PAK5. By "specific binding affinity" is meant that the antibody binds to the target kinase  
25       polypeptide with greater affinity than it binds to other polypeptides under specified conditions. Antibodies or antibody fragments are polypeptides that contain regions that can bind other polypeptides. The term "specific binding affinity" describes an antibody that binds to a kinase polypeptide with greater affinity than it binds to  
30       other polypeptides under specified conditions.

          The term "polyclonal" refers to antibodies that are heterogenous populations of antibody molecules derived from the sera of animals immunized with an antigen or an

antigenic functional derivative thereof. For the production of polyclonal antibodies, various host animals may be immunized by injection with the antigen. Various adjuvants may be used to increase the immunological response, depending on the host species.

"Monoclonal antibodies" are substantially homogenous populations of antibodies to a particular antigen. They may be obtained by any technique which provides for the production of antibody molecules by continuous cell lines in culture. Monoclonal antibodies may be obtained by methods known to those skilled in the art (Kohler et al., Nature 256:495-497, 1975, and U.S. Patent No. 4,376,110, both of which are hereby incorporated by reference herein in their entirety including any figures, tables, or drawings).

The term "antibody fragment" refers to a portion of an antibody, often the hyper variable region and portions of the surrounding heavy and light chains, that displays specific binding affinity for a particular molecule. A hyper variable region is a portion of an antibody that physically binds to the polypeptide target.

Antibodies or antibody fragments having specific binding affinity to a kinase polypeptide of the invention may be used in methods for detecting the presence and/or amount of kinase polypeptide in a sample by probing the sample with the antibody under conditions suitable for kinase-antibody immunocomplex formation and detecting the presence and/or amount of the antibody conjugated to the kinase polypeptide. Diagnostic kits for performing such methods may be constructed to include antibodies or antibody fragments specific for the kinase as well as a conjugate of a binding partner of the antibodies or the antibodies themselves.

An antibody or antibody fragment with specific binding affinity to a kinase polypeptide of the invention can be isolated, enriched, or purified from a prokaryotic or eukaryotic organism. Routine methods known to those skilled in the art enable production of antibodies or antibody fragments, in both prokaryotic and eukaryotic organisms. Purification, enrichment, and isolation of antibodies, which are polypeptide molecules, are described above.

Antibodies having specific binding affinity to a kinase polypeptide of the invention may be used in methods for detecting the presence and/or amount of kinase polypeptide in a sample by contacting the sample with the antibody under conditions such that an immunocomplex forms and detecting the presence and/or amount of the antibody conjugated to the kinase polypeptide. Diagnostic kits for performing such methods may be constructed to include a first container containing the antibody and a second container having a conjugate of a binding partner of the antibody and a label, such as, for example, a radioisotope. The diagnostic kit may also include notification of an FDA approved use and instructions therefor.

In a sixth aspect, the invention features a hybridoma which produces an antibody having specific binding affinity to a kinase polypeptide or a kinase polypeptide domain, where the polypeptide is selected from the group consisting of STLK2, STLK3, STLK4, STLK5, STLK6, STLK7, ZC1, ZC2, ZC3, ZC4, KHS2, SULU1, SULU3, GEK2, PAK4, and PAK5. By "hybridoma" is meant an immortalized cell line that is capable of secreting an antibody, for example an antibody to a kinase of the invention. In preferred embodiments, the antibody to the kinase comprises a sequence of amino acids that is able to specifically bind a kinase polypeptide of the invention.

In a seventh aspect, the invention features a kinase polypeptide binding agent able to bind to a kinase polypeptide selected from the group consisting of STLK2, STLK3, STLK4, STLK6, STLK7, STLK5, ZC1, ZC2, ZC3, ZC4, KHS2, SULU1, SULU3, GEK2, PAK4, and PAK5. The binding agent is preferably a purified antibody that recognizes an epitope present on a kinase polypeptide of the invention. Other binding agents include molecules that bind to kinase polypeptides and analogous molecules that bind to a kinase polypeptide. Such binding agents may be identified by using assays that measure kinase binding partner activity, such as those that measure PDGFR activity.

The invention also features a method for screening for human cells containing a kinase polypeptide of the invention or an equivalent sequence. The method involves identifying the novel polypeptide in human cells using techniques that are routine and standard in the art, such as those described herein for identifying the kinases of the invention (e.g., cloning, Southern or Northern blot analysis, in situ hybridization, PCR amplification, etc.).

In an eighth aspect, the invention features methods for identifying a substance that modulates kinase activity comprising the steps of: (a) contacting a kinase polypeptide selected from the group consisting of STLK2, STLK3, STLK4, STLK5, STLK6, STLK7, ZC1, ZC2, ZC3, ZC4, KHS2, SULU1, SULU3, GEK2, PAK4, and PAK5 with a test substance; (b) measuring the activity of said polypeptide; and (c) determining whether said substance modulates the activity of said polypeptide.

The term "modulates" refers to the ability of a compound to alter the function of a kinase of the invention.

A modulator preferably activates or inhibits the activity



of a kinase of the invention depending on the concentration of the compound exposed to the kinase.

The term "activates" refers to increasing the cellular activity of the kinase. The term inhibit refers to  
5 decreasing the cellular activity of the kinase. Kinase activity is preferably the interaction with a natural binding partner.

The term "modulates" also refers to altering the function of kinases of the invention by increasing or  
10 decreasing the probability that a complex forms between the kinase and a natural binding partner. A modulator preferably increases the probability that such a complex forms between the kinase and the natural binding partner, more preferably increases or decreases the probability that  
15 a complex forms between the kinase and the natural binding partner depending on the concentration of the compound exposed to the kinase, and most preferably decreases the probability that a complex forms between the kinase and the natural binding partner.

The term "complex" refers to an assembly of at least two molecules bound to one another. Signal transduction complexes often contain at least two protein molecules bound to one another. For instance, a protein tyrosine receptor protein kinase, GRB2, SOS, RAF, and RAS assemble to form a  
20 signal transduction complex in response to a mitogenic ligand.  
25

The term "natural binding partner" refers to polypeptides, lipids, small molecules, or nucleic acids that bind to kinases in cells. A change in the interaction  
30 between a kinase and a natural binding partner can manifest itself as an increased or decreased probability that the interaction forms, or an increased or decreased concentration of kinase/natural binding partner complex.

The term "contacting" as used herein refers to mixing a solution comprising the test compound with a liquid medium bathing the cells of the methods. The solution comprising the compound may also comprise another component, such as dimethyl sulfoxide (DMSO), which facilitates the uptake of the test compound or compounds into the cells of the methods. The solution comprising the test compound may be added to the medium bathing the cells by utilizing a delivery apparatus, such as a pipet-based device or syringe-based device.

In a ninth aspect, the invention features methods for identifying a substance that modulates kinase activity in a cell comprising the steps of: (a) expressing a kinase polypeptide in a cell, wherein said polypeptide is selected from the group consisting of STLK2, STLK3, STLK4, STLK5, STLK6, STLK7, ZC1, ZC2, ZC3, ZC4, KHS2, SULU1, SULU3, GEK2, PAK4, and PAK5; (b) adding a test substance to said cell; and (c) monitoring a change in cell phenotype or the interaction between said polypeptide and a natural binding partner.

The term "expressing" as used herein refers to the production of kinases of the invention from a nucleic acid vector containing kinase genes within a cell. The nucleic acid vector is transfected into cells using well known techniques in the art as described herein.

In a tenth aspect, the invention provides methods for treating a disease by administering to a patient in need of such treatment a substance that modulates the activity of a kinase selected from the group consisting of STLK2, STLK3, STLK4, STLK5, STLK6, STLK7, ZC1, ZC2, ZC3, ZC4, KHS2, SULU1, SULU3, GEK2, PAK4, and PAK5. Preferably, the disease is selected from the group consisting of immune-related diseases and disorders, organ transplantation, myocardial

infarction, cardiovascular disease, stroke, renal failure, oxidative stress-related neurodegenerative disorders, and cancer. Most preferably, the immune-related diseases and disorders include, but are not limited to, rheumatoid arthritis, arteriosclerosis, and autoimmune disorders.

In preferred embodiments, the invention provides methods for treating or preventing a disease or disorder by administering to a patient in need of such treatment a substance that modulates the activity of a kinase polypeptide selected from the group consisting of ZC1, ZC2, ZC3, ZC4, KHS2, PAK4, and PAK5. Preferably, the disease or disorder is selected from the group consisting of rheumatoid arthritis, arteriosclerosis, autoimmune disorders, and organ transplantation. The invention also features methods of treating or preventing a disease or disorder by administering to a patient in need of such treatment a substance that modulates the activity of a kinase polypeptide selected from the group consisting of STLK1, STLK2, STLK3, STLK4, STLK5, STLK6, and STLK7. Preferably the disease or disorder is selected from the group consisting of immune-related diseases and disorders, myocardial infarction, cardiomyopathies, stroke, renal failure, and oxidative stress-related neurodegenerative disorders. Most preferably, the immune-related diseases and disorders are selected from the group consisting of rheumatoid arthritis, chronic inflammatory bowel disease, chronic inflammatory pelvic disease, multiple sclerosis, asthma, osteoarthritis, psoriasis, arteriosclerosis, rhinitis, autoimmunity, and organ transplantation.

The invention also features methods of treating or preventing a disease or disorder by administering to a patient in need of such treatment a substance that modulates the activity of a kinase polypeptide selected from the group

consisting of ZC1, ZC2, ZC3, and ZC4. Preferably the disease is selected from the group consisting of immune-related diseases and disorders, cardiovascular disease, and cancer. Most preferably, the immune-related diseases and disorders are selected from the group consisting of rheumatoid arthritis, chronic inflammatory bowel disease, chronic inflammatory pelvic disease, multiple sclerosis, asthma, osteoarthritis, psoriasis, atherosclerosis, rhinitis, autoimmunity, and organ transplantation.

Substances useful for treatment of kinase-related disorders or diseases preferably show positive results in one or more *in vitro* assays for an activity corresponding to treatment of the disease or disorder in question (Examples of such assays are provided in the references in section VI, below; and in Example 7, herein). Examples of substances that can be screened for favorable activity are provided and referenced in section VI, below. The substances that modulate the activity of the kinases preferably include, but are not limited to, antisense oligonucleotides and inhibitors of protein kinases, as determined by methods and screens referenced in section VI and Example 7, below.

The term "preventing" refers to decreasing the probability that an organism contracts or develops an abnormal condition.

The term "treating" refers to having a therapeutic effect and at least partially alleviating or abrogating an abnormal condition in the organism.

The term "therapeutic effect" refers to the inhibition or activation factors causing or contributing to the abnormal condition. A therapeutic effect relieves to some extent one or more of the symptoms of the abnormal condition. In reference to the treatment of abnormal conditions, a therapeutic effect can refer to one or more of

the following: (a) an increase in the proliferation, growth, and/or differentiation of cells; (b) inhibition (i.e., slowing or stopping) of cell death; (c) inhibition of degeneration; (d) relieving to some extent one or more of the symptoms associated with the abnormal condition; and (e) enhancing the function of the affected population of cells.

Compounds demonstrating efficacy against abnormal conditions can be identified as described herein.

The term "abnormal condition" refers to a function in the cells or tissues of an organism that deviates from their normal functions in that organism. An abnormal condition can relate to cell proliferation, cell differentiation, or cell survival.

Abnormal cell proliferative conditions include cancers such as fibrotic and mesangial disorders, abnormal angiogenesis and vasculogenesis, wound healing, psoriasis, diabetes mellitus, and inflammation.

Abnormal differentiation conditions include, but are not limited to neurodegenerative disorders, slow wound healing rates, and slow tissue grafting healing rates.

Abnormal cell survival conditions relate to conditions in which programmed cell death (apoptosis) pathways are activated or abrogated. A number of protein kinases are associated with the apoptosis pathways. Aberrations in the function of any one of the protein kinases could lead to cell immortality or premature cell death.

The term "aberration", in conjunction with the function of a kinase in a signal transduction process, refers to a kinase that is over- or under-expressed in an organism, mutated such that its catalytic activity is lower or higher than wild-type protein kinase activity, mutated such that it can no longer interact with a natural binding partner, is no longer modified by another protein kinase or protein

phosphatase, or no longer interacts with a natural binding partner.

The term "administering" relates to a method of incorporating a compound into cells or tissues of an organism. The abnormal condition can be prevented or treated when the cells or tissues of the organism exist within the organism or outside of the organism. Cells existing outside the organism can be maintained or grown in cell culture dishes. For cells harbored within the organism, many techniques exist in the art to administer compounds, including (but not limited to) oral, parenteral, dermal, injection, and aerosol applications. For cells outside of the organism, multiple techniques exist in the art to administer the compounds, including (but not limited to) cell microinjection techniques, transformation techniques, and carrier techniques.

The abnormal condition can also be prevented or treated by administering a compound to a group of cells having an aberration in a signal transduction pathway to an organism.

The effect of administering a compound on organism function can then be monitored. The organism is preferably a mouse, rat, rabbit, guinea pig, or goat, more preferably a monkey or ape, and most preferably a human.

In an eleventh aspect, the invention features methods for detection of a kinase polypeptide in a sample as a diagnostic tool for diseases or disorders, wherein the method comprises the steps of: (a) contacting the sample with a nucleic acid probe which hybridizes under hybridization assay conditions to a nucleic acid target region of a kinase polypeptide selected from the group consisting of STLK2, STLK3, STLK4, STLK5, STLK6, STLK7, ZC1, ZC2, ZC3, ZC4, KHS2, SULU1, SULU3, GEK2, PAK4, and PAK5, said probe comprising the nucleic acid sequence encoding the

polypeptide, fragments thereof, and the complements of the sequences and fragments; and (b) detecting the presence or amount of the probe:target region hybrid as an indication of the disease.

5 In preferred embodiments of the invention, the disease or disorder is selected from the group consisting of rheumatoid arthritis, arteriosclerosis, autoimmune disorders, organ transplantation, myocardial infarction, cardiomyopathies, stroke, renal failure, oxidative stress-  
10 related neurodegenerative disorders, and cancer. In other preferred embodiments, the kinase polypeptide is selected from the group consisting of PAK4 and PAK5, or the polypeptide is selected from the group consisting of ZC1, ZC2, ZC3, and ZC4, and the disease is cancer.

15 The kinase "target region" is the nucleotide base sequence set forth in SEQ ID NO:1, SEQ ID NO:2, SEQ ID NO:3, SEQ ID NO:9, SEQ ID NO:10, SEQ ID NO:11, SEQ ID NO:17, SEQ ID NO:19, SEQ ID NO:20, SEQ ID NO:21, SEQ ID NO:27, SEQ ID NO:96, SEQ ID NO:98, SEQ ID NO:100, SEQ ID NO:102, SEQ ID  
20 NO:104, or SEQ ID NO:106, or the corresponding full-length sequences, a functional derivative thereof, or a fragment thereof to which the nucleic acid probe will specifically hybridize. Specific hybridization indicates that in the presence of other nucleic acids the probe only hybridizes  
25 detectably with the kinase of the invention's target region.

Putative target regions can be identified by methods well known in the art consisting of alignment and comparison of the most closely related sequences in the database.

In preferred embodiments the nucleic acid probe  
30 hybridizes to a kinase target region encoding at least 6, 12, 75, 90, 105, 120, 150, 200, 250, 300 or 350 contiguous amino acids of the sequence set forth in SEQ ID NO:5, SEQ ID NO:6, SEQ ID NO:7, SEQ ID NO:13, SEQ ID NO:14, SEQ ID NO:15,

SEQ ID NO:18, SEQ ID NO:22, SEQ ID NO:23, SEQ ID NO:24, SEQ ID NO:29, SEQ ID NO:31, SEQ ID NO:97, SEQ ID NO:99, SEQ ID NO:101, SEQ ID NO:103, SEQ ID NO:105, or SEQ ID NO:107, or the corresponding full-length amino acid sequence, or a functional derivative thereof. Hybridization conditions should be such that hybridization occurs only with the kinase genes in the presence of other nucleic acid molecules. Under stringent hybridization conditions only highly complementary nucleic acid sequences hybridize. Preferably, such conditions prevent hybridization of nucleic acids having more than 1 or 2 mismatches out of 20 contiguous nucleotides. Such conditions are defined supra.

The diseases for which detection of kinase genes in a sample could be diagnostic include diseases in which kinase nucleic acid (DNA and/or RNA) is amplified in comparison to normal cells. By "amplification" is meant increased numbers of kinase DNA or RNA in a cell compared with normal cells. In normal cells, kinases are typically found as single copy genes. In selected diseases, the chromosomal location of the kinase genes may be amplified, resulting in multiple copies of the gene, or amplification. Gene amplification can lead to amplification of kinase RNA, or kinase RNA can be amplified in the absence of kinase DNA amplification.

"Amplification" as it refers to RNA can be the detectable presence of kinase RNA in cells, since in some normal cells there is no basal expression of kinase RNA. In other normal cells, a basal level of expression of kinase exists, therefore in these cases amplification is the detection of at least 1-2-fold, and preferably more, kinase RNA, compared to the basal level.

The diseases that could be diagnosed by detection of kinase nucleic acid in a sample preferably include cancers. The test samples suitable for nucleic acid probing methods



of the present invention include, for example, cells or nucleic acid extracts of cells, or biological fluids. The samples used in the above-described methods will vary based on the assay format, the detection method and the nature of the tissues, cells or extracts to be assayed. Methods for preparing nucleic acid extracts of cells are well known in the art and can be readily adapted in order to obtain a sample that is compatible with the method utilized.

In a final aspect, the invention features a method for detection of a kinase polypeptide in a sample as a diagnostic tool for a disease or disorder, wherein the method comprises: (a) comparing a nucleic acid target region encoding the kinase polypeptide in a sample, where the kinase polypeptide is selected from the group consisting of STLK2, STLK3, STLK4, STLK5, STLK6, STLK7, ZC1, ZC2, ZC3, ZC4, KHS2, SULU1, SULU3, GEK2, PAK4, and PAK5, or one or more fragments thereof, with a control nucleic acid target region encoding the kinase polypeptide, or one or more fragments thereof; and (b) detecting differences in sequence or amount between the target region and the control target region, as an indication of the disease or disorder. Preferably, the disease or disorder is selected from the group consisting of immune-related diseases and disorders, organ transplantation, myocardial infarction, cardiovascular disease, stroke, renal failure, oxidative stress-related neurodegenerative disorders, and cancer. Immune-related diseases and disorders include, but are not limited to, those discussed previously.

The term "comparing" as used herein refers to identifying discrepancies between the nucleic acid target region isolated from a sample, and the control nucleic acid target region. The discrepancies can be in the nucleotide sequences, e.g. insertions, deletions, or point mutations,

or in the amount of a given nucleotide sequence. Methods to determine these discrepancies in sequences are well-known to one of ordinary skill in the art. The "control" nucleic acid target region refers to the sequence or amount of the sequence found in normal cells, e.g. cells that are not diseased as discussed previously.

The invention has been described broadly and generically herein. Each of the narrower species and subgeneric groupings falling within the generic disclosure also form part of the invention. This includes the generic description of the invention with a proviso or negative limitation removing any subject matter from the genus, regardless of whether or not the excised material is specifically recited herein. For example, in some instances the nucleotide sequence of the ZC4 kinase polypeptide may not be part of a preferred embodiment.

The summary of the invention described above is not limiting and other features and advantages of the invention will be apparent from the following detailed description of the invention, and from the claims.

#### BRIEF DESCRIPTION OF THE FIGURES

Figure 1 shows a multiple sequence alignment of the amino acid sequences of the STE20-STE20 family kinases.

Figure 2 shows a multiple sequence alignment of the amino acid sequences of the STE20-STLK5 family kinases.

Figures 3A and 3B show a multiple sequence alignment of the amino acid sequences of STE20-ZC family kinases.

Figure 4 shows a pairwise sequence alignment of STE20-KHS family kinases.

Figure 5 shows a multiple sequence alignment of the amino acid sequences of STE20-SULU family kinases.

Figure 6 shows a pairwise sequence alignment of STE20-GEK family kinases

Figure 7 shows a multiple sequence alignment of the amino acid sequences of STE20-PAK family kinases.

5        Figures 8A, 8B, 8C, 8D, and 8E show the amino acid sequences of human STLK2, human STLK3, human STLK4, human STLK5, human ZC1, human ZC2, human ZC3, human ZC4, human KHS2, human SULU1, human SULU3, murine SULU3, human GEK2, human PAK4, and human PAK5.

10        Figures 9A, 9B, 9C, 9D, 9E, 9F, 9G, 9H, 9I, 9J, 9K, 9L, 9M, 9N, 9O, and 9P show the nucleic acid sequences of human STLK2, human STLK3, human STLK4, human STLK5, human ZC1, human ZC2, human ZC3, human ZC4, human KHS2, human SULU1, human SULU3, murine SULU3, human GEK2, human PAK4, and human  
15        PAK5.

      Figures 10A and 10B show the full-length amino acid sequences of human STLK5 (SEQ ID NO: 97), human PAK5 (SEQ ID NO:103), and human ZC4 (SEQ ID NO:105), as well as the partial amino acid sequences of human full-length STLK6 (SEQ  
20        ID NO: 99) and human STLK7 (SEQ ID NO: 101).

      Figures 11A, 11B, 11C, and 11D show the full-length nucleic acid sequences of human STLK5 (SEQ ID NO:96), human PAK5 (SEQ ID NO:102), and human ZC4 (SEQ ID NO:104), as well as the partial nucleic acid sequences of human STLK6 (SEQ ID  
25        NO: 98) and human STLK7 (SEQ ID NO: 100).

      Figure 12 shows a multiple sequence alignment among human SPAK, human STLK6, human STLK7 and full-length human STLK5.

      Figure 13 shows a multiple sequence alignment among  
30        human PAK1, human PAK4 and human PAK5.

      Figures 14A and 14B show a pair-wise sequence alignment between human ZC1 and human ZC4.

Figure 15 shows a pair-wise sequence alignment between LOK1 and full-length GEK2.

#### DETAILED DESCRIPTION OF THE INVENTION

5           The present invention relates in part to kinase polypeptides, nucleic acids encoding such polypeptides, cells containing such nucleic acids, antibodies to such polypeptides, assays utilizing such polypeptides, and methods relating to all of the foregoing. The present  
10          invention is based upon the isolation and characterization of new kinase polypeptides. The polypeptides and nucleic acids may be produced using well-known and standard synthesis techniques when given the sequences presented herein.

15           The recent elucidation of the DNA sequence of *Saccharomyces cerevesiae* has provided the first complete example of the genetic information contained in a simple eukaryotic organism. Analysis of this yeast genome revealed that it contains at least 113 protein kinases. These  
20          kinases were further subdivided into several structurally related groups. One of these newly defined groups was termed the STE20-family to represent its founding member STE20, which is a protein kinase involved in the yeast pheromone response pathway that initiates a protein kinase  
25          cascade in response to a G-protein mediated signal. *S. cerevesiae* has two additional members of this family, CLA4, and YOL113W (HRA655).

          Several mammalian homologues have recently been identified that belong to the STE20-family, including SOK-1  
30          (human STE20), GC-kinase, KHS, HPK1, NIK, SLK, GEK, PAK1, PAK65, MST1, and CDC7. Furthermore, the *Drosophila* and the *C. elegans* genome efforts have identified additional protein kinases which belong to the STE20-family, yet have

structurally unique extracatalytic domains, including ZC504.4 and SULU kinases from *C. elegans*, and NINAC of *Drosophila*.

STE20-related protein kinases have been implicated as  
5 regulating a variety of cellular responses, including  
response to growth factors or cytokines, oxidative-, UV-, or  
irradiation-related stress pathways, inflammatory signals  
(i.e., TNF $\alpha$ ), apoptotic stimuli (i.e., Fas), T and B cell  
costimulation, the control of cytoskeletal architecture, and  
10 cellular transformation. Typically, the STE20-related  
kinases serve as upstream regulators of MAPK cascades.  
Examples include: HPK1, a protein-serine/ threonine kinase  
(STK) that possesses a STE20-like kinase domain that  
activates a protein kinase pathway leading to the stress-  
15 activated protein kinase SAPK/JNK; PAK1, an STK with an  
upstream CDC42-binding domain that interacts with Rac and  
plays a role in cellular transformation through the Ras-MAPK  
pathway; and murine NIK, which interacts with upstream  
receptor tyrosine kinases and connects with downstream  
20 STE11-family kinases.

The STE20-kinases possess a variety of non-catalytic  
domains that are believed to interact with upstream  
regulators. Examples include proline-rich domains for  
interaction with SH3-containing proteins, or specific  
25 domains for interaction with Rac, Rho, and Rab small G-  
proteins. These interactions may provide a mechanism for  
cross-talk between distinct biochemical pathways in response  
to external stimuli such as the activation of a variety of  
cell surface receptors, including tyrosine kinases, cytokine  
30 receptors, TNF receptor, Fas, T cell receptors, CD28, or  
CD40.

I. The Nucleic Acids of the Invention

Included within the scope of this invention are the functional equivalents of the herein-described isolated nucleic acid molecules. The degeneracy of the genetic code permits substitution of certain codons by other codons that specify the same amino acid and hence would give rise to the same protein. The nucleic acid sequence can vary substantially since, with the exception of methionine and tryptophan, the known amino acids can be coded for by more than one codon. Thus, portions or all of the kinase genes of the invention could be synthesized to give a nucleic acid sequence significantly different from that shown in SEQ ID NO:1, SEQ ID NO:2, SEQ ID NO:3, SEQ ID NO:9, SEQ ID NO:10, SEQ ID NO:11, SEQ ID NO:17, SEQ ID NO:19, SEQ ID NO:20, SEQ ID NO:21, SEQ ID NO:27, SEQ ID NO:96, SEQ ID NO:98, SEQ ID NO:100, SEQ ID NO:102, SEQ ID NO:104, and SEQ ID NO:106. The encoded amino acid sequence thereof would, however, be preserved.

In addition, the nucleic acid sequence may comprise a nucleotide sequence which results from the addition, deletion or substitution of at least one nucleotide to the 5'-end and/or the 3'-end of the nucleic acid formula shown in SEQ ID NO:1, SEQ ID NO:2, SEQ ID NO:3, SEQ ID NO:9, SEQ ID NO:10, SEQ ID NO:11, SEQ ID NO:17, SEQ ID NO:19, SEQ ID NO:20, SEQ ID NO:21, SEQ ID NO:27, SEQ ID NO:96, SEQ ID NO:98, SEQ ID NO:100, SEQ ID NO:102, SEQ ID NO:104, or SEQ ID NO:106, or a derivative thereof. Any nucleotide or polynucleotide may be used in this regard, provided that its addition, deletion or substitution does not alter the amino acid sequence of SEQ ID NO:5, SEQ ID NO:6, SEQ ID NO:7, SEQ ID NO:13, SEQ ID NO:14, SEQ ID NO:15, SEQ ID NO:18, SEQ ID NO:22, SEQ ID NO:23, SEQ ID NO:24, SEQ ID NO:29, SEQ ID NO:97, SEQ ID NO:99, SEQ ID NO:101, SEQ ID NO:103, SEQ ID

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NO:105, or SEQ ID NO:107, which is encoded by the nucleotide sequence. For example, the present invention is intended to include any nucleic acid sequence resulting from the addition of ATG as an initiation codon at the 5'-end of the inventive nucleic acid sequence or its derivative, or from the addition of TTA, TAG or TGA as a termination codon at the 3'-end of the inventive nucleotide sequence or its derivative. Moreover, the nucleic acid molecule of the present invention may, as necessary, have restriction endonuclease recognition sites added to its 5'-end and/or 3'-end.

Such functional alterations of a given nucleic acid sequence afford an opportunity to promote secretion and/or processing of heterologous proteins encoded by foreign nucleic acid sequences fused thereto. All variations of the nucleotide sequence of the kinase genes of the invention and fragments thereof permitted by the genetic code are, therefore, included in this invention.

Further, it is possible to delete codons or to substitute one or more codons with codons other than degenerate codons to produce a structurally modified polypeptide, but one which has substantially the same utility or activity as the polypeptide produced by the unmodified nucleic acid molecule. As recognized in the art, the two polypeptides are functionally equivalent, as are the two nucleic acid molecules that give rise to their production, even though the differences between the nucleic acid molecules are not related to the degeneracy of the genetic code.

#### Mammalian STLK2

The full-length human STLK2 cDNA (SEQ ID NO:1) is 3268 bp long and consists of a 1248 bp open reading frame (ORF)

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flanked by a 181 bp 5' untranslated region (UTR; 1-181) and a 1784 bp 3' UTR (1433-3216) that is followed by a 52 nucleotide polyadenylated region. A polyadenylation signal (AATAAA) is found at positions (3193-3198). The sequence flanking the first ATG conforms to the Kozak consensus (Kozak, M., Nucleic Acids Res. 15, 8125-8148 (1987)) for an initiating methionine, and is believed to be the translational start site for STLK2. Furthermore, human STLK2 and the related SOK-1 and MST3 proteins conserve the amino acid sequence immediately following this presumed initiating methionine.

Several EST fragments span the complete STLK2 sequence with AA191319 at the 5' end and W16504 at the 3' end.

#### Mammalian STLK3

The partial human STLK3 cDNA (SEQ ID NO:2) is 3030 bp long and consists of a 1548 bp ORF flanked by a 1476 bp 3' UTR (1550-3025) and a 5 nucleotide polyadenylated region. A potential polyadenylation signal (AATAAA) begins at position 3004. Since the coding region is open throughout the 5' extent of this sequence, this is apparently a partial cDNA clone lacking the N-terminal start methionine.

Multiple EST fragments span the complete STLK3 sequence with AA278967 at the 5' end and AA628477 and others at the 3' end.

#### Mammalian STLK4

The partial human STLK4 cDNA (SEQ ID NO:3) is 3857 bp long and consists of a 1242 bp ORF flanked by a 2596 bp 3' UTR (1244-3839) and an 18 nucleotide polyadenylated region. A potential polyadenylation signal (AATAAA) is found at positions 2181-3822. Since the coding region is open throughout the 5' extent of this sequence, this is



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apparently a partial cDNA clone lacking the N-terminal start methionine. A near full-length murine STLK4 cDNA is represented in the 1773 bp EST AA117438. It extends an additional 21 nucleotides 5' of the human STLK4 consensus, but since its coding region is open throughout the 5' extent of the sequence, this is also apparently a partial cDNA clone lacking the N-terminal start methionine.

Several EST fragments span the complete STLK3 sequence with AA297759 at the 5' end and AA100484 and others at the 3' end.

#### Mammalian STLK5

The full-length human STLK5 cDNA (SEQ ID NO:96) is 2110 bp long and consists of a 1119 bp ORF flanked by a 229 bp 5' UTR and a 762 bp 3' UTR. The sequence flanking the first ATG conforms to the Kozak consensus (supra) for an initiating methionine, and is believed to be the translational start site for STLK5. Several EST fragments span the complete STLK5 sequence with AA297059 and F07734 at the 5' end, and R46686 and F03423 and others at the 3' end.

#### Mammalian STLK6

The full-length human STLK6 cDNA (SEQ ID NO:98) is 2,001 bp long and consists of a 1,254 bp ORF flanked by a 75 bp 5' UTR and a 673 bp 3' UTR. The sequence flanking the first ATG conforms to the Kozak consensus (supra) for an initiating methionine, and is believed to be the translational start site for STLK6.

#### Mammalian STLK7

The partial human STLK7 cDNA (SEQ ID NO:100) is 311 bp long and consists of a 309 bp ORF. Since the coding region is open throughout both the 5' and 3' extent of this

sequence, this is apparently a partial cDNA clone lacking the N-terminal start methionine and C-terminal stop codon.

#### Mammalian ZC1

5           The full-length human ZC1 cDNA (SEQ ID NO:9) is 3798 bp long and consists of a 3717 bp ORF (7-3723) flanked by a 6 bp 5' UTR and a 75 bp (3724-3798) 3' UTR. No polyadenylation signal (AATAAA) or polyadenylated region are present in the 3'UTR. The sequence flanking the first ATG  
10 conforms to the Kozak consensus for an initiating methionine, and is believed to be the translational start site for human ZC1.

          Multiple EST fragments (W81656) match the 3' end of the human ZC1 gene, but at the time of filing, the inventors  
15 believe that none exist in GenBank or the EST database that match its 5' end.

#### Mammalian ZC2

          The partial human ZC2 cDNA (SEQ ID NO:10) is 4055 bp  
20 long and consists of a 3891 bp ORF (1-3891) and a 164 bp (3892-4055) 3' UTR. Since the coding region is open throughout the 5' extent of this sequence, this is apparently a partial cDNA clone lacking the N-terminal start methionine. No polyadenylation signal (AATAAA) or  
25 polyadenylated region are present in the 3'UTR.

          Multiple EST fragments (R51245) match the 3' end of the human ZC2 gene, but at the time of filing, the inventors believe that none exist in GenBank or the EST database that match its 5' end.

#### Mammalian ZC3

          The partial human ZC3 cDNA (SEQ ID NO:11) is 4133 bp long and consists of a 3978 bp ORF (1-3978) and a 152 bp

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(3979-4133) 3'UTR region. Since the coding region is open throughout the 5' extent of this sequence, this is apparently a partial cDNA clone lacking the N-terminal start methionine. No polyadenylation signal (AATAAA) or polyadenylated region are present in the 3'UTR.

Multiple EST fragments (R54563) match the 3'end of the human ZC3 gene, but at the time of filing, the inventors believe that none exist in GenBank or the EST database that match its 5' end.

#### Mammalian ZC4

The full-length human ZC4 cDNA (SEQ ID NO:104) is 3,684 bp long and was originally assembled from X chromosome genomic DNA sequence.

Multiple EST fragments (R98571) match the 3'end of the human ZC4 gene, but at the time of filing, the inventors believe that none exist in GenBank or the EST database that match its 5' end. ZC4 gene is also contained within the human genomic clone Z83850.

#### Mammalian KHS2

The full-length human KHS2 cDNA (SEQ ID NO:17) is 4023 bp long and consists of a 2682 bp ORF (6-2687) flanked by a 5 bp (1-5) 5'UTR and a 1336 bp (2688-4023) 3' UTR. A potential polyadenylation signal (AATAAA) is found at positions 4008-4013. No polyadenylated region is present in the 3'UTR. The sequence flanking the first ATG conforms to the Kozak consensus for an initiating methionine, and is believed to be the translational start site for human KHS2.

Multiple EST fragments match the 5'end (AA446022) as well as the 3' end (R37625) of the human KHS2 gene.

Mammalian SULU1

The full-length human SULU1 cDNA (SEQ ID NO:19) is 4177 bp long and consists of a 2694 bp ORF (415-3108) flanked by a 414 bp (1-414) 5'UTR and a 1069 bp (3109-4177) 3' UTR followed by a 19 nucleotide polydenylated region. A potential polyadenylation signal (AATAAA) is found at positions 4164-4169. The sequence flanking the first ATG conforms to the Kozak consensus for an initiating methionine, and is believed to be the translational start site for human SULU1.

Multiple EST fragments match the 5'end (N27153) as well as the 3' end (R90908) of the human SULU1 gene.

Mammalian (Murine) SULU3

The partial murine SULU3 cDNA (SEQ ID NO:21) is 2249 bp long and consists of a 2244 bp ORF (6-2249) flanked by a 5 bp (1-5) 5'UTR. The sequence flanking the first ATG conforms to the Kozak consensus for an initiating methionine, and is believed to be the translational start site for murine SULU3. The 3' end of the murine SULU3 cDNA shares 90% DNA sequence identity over 1620 nucleotides with human SULU3, suggesting that these two genes are functional orthologues.

One EST fragment (AA446022) matches the 3' end of the partial murine SULU3 gene, but at the time of filing, the inventors believe that none exist in GenBank or the EST database that match its 5' end.

Mammalian (Human) SULU3

The partial human SULU3 cDNA (SEQ ID NO:20) is 3824 bp long and consists of a 2358 bp ORF (2-2359) flanked by a 1465 bp (2360-3824) 3'UTR followed by a 19 nucleotide polydenylated region. A potential polyadenylation signal

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(AATAAA) is found at positions 2602-2607. Since the coding region is open throughout the 5' extent of this sequence, this is apparently a partial cDNA clone lacking the N-terminal start methionine. The 5' end of the human SULU3 cDNA shares 90% DNA sequence identity over 1620 nucleotides with murine SULU3, suggesting that these two genes are functional orthologues.

Multiple EST fragments (R02283) match the 3' end of the human SULU3 gene, but at the time of filing, the inventors believe that none exist in GenBank or the EST database that match its 5' end.

#### Mammalian GEK2

The full-length human GEK2 cDNA (SEQ ID NO:106) is 2962 bp long and consists of a 2737 bp ORF (59-2795) flanked by a 58 bp (1-58) 5'UTR. The sequence flanking the first ATG conforms to the Kozak consensus for an initiating methionine, and is believed to be the translational start site for human GEK2.

Multiple EST fragments (AA465671) match the 5' end, but at the time of filing, the inventors believe that only one (AA380492) matches the 3' end of the human GEK2 gene.

#### Mammalian PAK4

The full-length human PAK4 cDNA (SEQ ID NO:27) is 3604 bp long and consists of a 2043 bp ORF (143-2185) flanked by a 142 bp (1-142) 5'UTR and a 1419 3' UTR followed by a 22 nucleotide polydenylated region. A potential polyadenylation signal (AATTAAA) is found at positions 3582-3588. The sequence flanking the first ATG conforms to the Kozak consensus for an initiating methionine, and is believed to be the translational start site for human PAK4.

Multiple EST fragments (AA535791) match the 3' end of the human PAK4 gene, but at the time of filing, the inventors believe that none exist in GenBank or the EST database that match its 5' end.

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#### Mammalian PAK5

The full-length human PAK5 cDNA (SEQ ID NO:102) is 2806 bp long and consists of a 1773 bp ORF flanked by a 201 bp 5' UTR and a 833 bp 3' UTR. The sequence flanking the first  
10 ATG conforms to the Kozak consensus (supra) for an initiating methionine, and is believed to be the translational start site for PAK5.

Multiple EST fragments (AA442867) match the 3' end of the human PAK5 gene, but at the time of filing, the  
15 inventors believe that none exist in GenBank or the EST database that match its 5' end.

#### II. Nucleic Acid Probes, Methods, and Kits for Detection of STE20-Related Kinases.

A nucleic acid probe of the present invention may be  
20 used to probe an appropriate chromosomal or cDNA library by usual hybridization methods to obtain other nucleic acid molecules of the present invention. A chromosomal DNA or cDNA library may be prepared from appropriate cells  
25 according to recognized methods in the art (cf. "Molecular Cloning: A Laboratory Manual", second edition, Cold Spring Harbor Laboratory, Sambrook, Fritsch, & Maniatis, eds., 1989).

In the alternative, chemical synthesis can be carried  
30 out in order to obtain nucleic acid probes having nucleotide sequences which correspond to N-terminal and C-terminal portions of the amino acid sequence of the polypeptide of interest. The synthesized nucleic acid probes may be used

as primers in a polymerase chain reaction (PCR) carried out in accordance with recognized PCR techniques, essentially according to PCR Protocols, "A Guide to Methods and Applications", Academic Press, Michael, *et al.*, eds., 1990, 5 utilizing the appropriate chromosomal or cDNA library to obtain the fragment of the present invention.

One skilled in the art can readily design such probes based on the sequence disclosed herein using methods of computer alignment and sequence analysis known in the art 10 ("Molecular Cloning: A Laboratory Manual", 1989, *supra*). The hybridization probes of the present invention can be labeled by standard labeling techniques such as with a radiolabel, enzyme label, fluorescent label, biotin-avidin label, chemiluminescence, and the like. After 15 hybridization, the probes may be visualized using known methods.

The nucleic acid probes of the present invention include RNA, as well as DNA probes, such probes being generated using techniques known in the art. The nucleic 20 acid probe may be immobilized on a solid support. Examples of such solid supports include, but are not limited to, plastics such as polycarbonate, complex carbohydrates such as agarose and sepharose, and acrylic resins, such as polyacrylamide and latex beads. Techniques for coupling 25 nucleic acid probes to such solid supports are well known in the art.

The test samples suitable for nucleic acid probing methods of the present invention include, for example, cells or nucleic acid extracts of cells, or biological fluids. 30 The samples used in the above-described methods will vary based on the assay format, the detection method and the nature of the tissues, cells or extracts to be assayed. Methods for preparing nucleic acid extracts of cells are

well known in the art and can be readily adapted in order to obtain a sample which is compatible with the method utilized.

One method of detecting the presence of nucleic acids of the invention in a sample comprises (a) contacting said sample with the above-described nucleic acid probe under conditions such that hybridization occurs, and (b) detecting the presence of said probe bound to said nucleic acid molecule. One skilled in the art would select the nucleic acid probe according to techniques known in the art as described above. Samples to be tested include but should not be limited to RNA samples of human tissue.

A kit for detecting the presence of nucleic acids of the invention in a sample comprises at least one container means having disposed therein the above-described nucleic acid probe. The kit may further comprise other containers comprising one or more of the following: wash reagents and reagents capable of detecting the presence of bound nucleic acid probe. Examples of detection reagents include, but are not limited to radiolabelled probes, enzymatic labeled probes (horseradish peroxidase, alkaline phosphatase), and affinity labeled probes (biotin, avidin, or streptavidin).

In detail, a compartmentalized kit includes any kit in which reagents are contained in separate containers. Such containers include small glass containers, plastic containers or strips of plastic or paper. Such containers allow the efficient transfer of reagents from one compartment to another compartment such that the samples and reagents are not cross-contaminated and the agents or solutions of each container can be added in a quantitative fashion from one compartment to another. Such containers will include a container which will accept the test sample, a container which contains the probe or primers used in the



assay, containers which contain wash reagents (such as phosphate buffered saline, Tris-buffers, and the like), and containers which contain the reagents used to detect the hybridized probe, bound antibody, amplified product, or the like. One skilled in the art will readily recognize that the nucleic acid probes described in the present invention can readily be incorporated into one of the established kit formats which are well known in the art.

10 III. DNA Constructs Comprising a STE20-Related Nucleic Acid Molecule and Cells Containing These Constructs.

The present invention also relates to a recombinant DNA molecule comprising, 5' to 3', a promoter effective to initiate transcription in a host cell and the above-described nucleic acid molecules. In addition, the present invention relates to a recombinant DNA molecule comprising a vector and an above-described nucleic acid molecule. The present invention also relates to a nucleic acid molecule comprising a transcriptional region functional in a cell, a sequence complementary to an RNA sequence encoding an amino acid sequence corresponding to the above-described polypeptide, and a transcriptional termination region functional in said cell. The above-described molecules may be isolated and/or purified DNA molecules.

25 The present invention also relates to a cell or organism that contains an above-described nucleic acid molecule and thereby is capable of expressing a polypeptide.

The polypeptide may be purified from cells which have been altered to express the polypeptide. A cell is said to be "altered to express a desired polypeptide" when the cell, through genetic manipulation, is made to produce a protein which it normally does not produce or which the cell normally produces at lower levels. One skilled in the art

can readily adapt procedures for introducing and expressing either genomic, cDNA, or synthetic sequences into either eukaryotic or prokaryotic cells.

5 A nucleic acid molecule, such as DNA, is said to be "capable of expressing" a polypeptide if it contains nucleotide sequences which contain transcriptional and translational regulatory information and such sequences are "operably linked" to nucleotide sequences which encode the polypeptide. An operable linkage is a linkage in which the  
10 regulatory DNA sequences and the DNA sequence sought to be expressed are connected in such a way as to permit gene sequence expression. The precise nature of the regulatory regions needed for gene sequence expression may vary from organism to organism, but shall in general include a  
15 promoter region which, in prokaryotes, contains both the promoter (which directs the initiation of RNA transcription) as well as the DNA sequences which, when transcribed into RNA, will signal synthesis initiation. Such regions will normally include those 5'-non-coding sequences involved with  
20 initiation of transcription and translation, such as the TATA box, capping sequence, CAAT sequence, and the like.

If desired, the non-coding region 3' to the sequence encoding a kinase of the invention may be obtained by the above-described methods. This region may be retained for  
25 its transcriptional termination regulatory sequences, such as termination and polyadenylation. Thus, by retaining the 3'-region naturally contiguous to the DNA sequence encoding a kinase of the invention, the transcriptional termination signals may be provided. Where the transcriptional  
30 termination signals are not satisfactorily functional in the expression host cell, then a 3' region functional in the host cell may be substituted.

Two DNA sequences (such as a promoter region sequence and a sequence encoding a kinase of the invention) are said to be operably linked if the nature of the linkage between the two DNA sequences does not (1) result in the  
5 introduction of a frame-shift mutation, (2) interfere with the ability of the promoter region sequence to direct the transcription of a gene sequence encoding a kinase of the invention, or (3) interfere with the ability of the gene  
10 sequence of a kinase of the invention to be transcribed by the promoter region sequence. Thus, a promoter region would be operably linked to a DNA sequence if the promoter were capable of effecting transcription of that DNA sequence. Thus, to express a gene encoding a kinase of the invention, transcriptional and translational signals recognized by an  
15 appropriate host are necessary.

The present invention encompasses the expression of a gene encoding a kinase of the invention (or a functional derivative thereof) in either prokaryotic or eukaryotic cells. Prokaryotic hosts are, generally, very efficient and  
20 convenient for the production of recombinant proteins and are, therefore, one type of preferred expression system for kinases of the invention. Prokaryotes most frequently are represented by various strains of *E. coli*. However, other microbial strains may also be used, including other  
25 bacterial strains.

In prokaryotic systems, plasmid vectors that contain replication sites and control sequences derived from a species compatible with the host may be used. Examples of suitable plasmid vectors may include pBR322, pUC118, pUC119  
30 and the like; suitable phage or bacteriophage vectors may include  $\gamma$ gt10,  $\gamma$ gt11 and the like; and suitable virus vectors may include pMAM-neo, pKRC and the like. Preferably, the

selected vector of the present invention has the capacity to replicate in the selected host cell.

Recognized prokaryotic hosts include bacteria such as *E. coli*, *Bacillus*, *Streptomyces*, *Pseudomonas*, *Salmonella*, *Serratia*, and the like. However, under such conditions, the polypeptide will not be glycosylated. The prokaryotic host must be compatible with the replicon and control sequences in the expression plasmid.

To express a kinase of the invention (or a functional derivative thereof) in a prokaryotic cell, it is necessary to operably link the sequence encoding the kinase of the invention to a functional prokaryotic promoter. Such promoters may be either constitutive or, more preferably, regulatable (*i.e.*, inducible or derepressible). Examples of constitutive promoters include the *int* promoter of bacteriophage  $\lambda$ , the *bla* promoter of the  $\beta$ -lactamase gene sequence of pBR322, and the *cat* promoter of the chloramphenicol acetyl transferase gene sequence of pPR325, and the like. Examples of inducible prokaryotic promoters include the major right and left promoters of bacteriophage  $\lambda$  ( $P_L$  and  $P_R$ ), the *trp*, *recA*, *lacZ*, *lacI*, and *gal* promoters of *E. coli*, the  $\alpha$ -amylase (Ulmanen *et al.*, *J. Bacteriol.* 162:176-182, 1985) and the  $\zeta$ -28-specific promoters of *B. subtilis* (Gilman *et al.*, *Gene Sequence* 32:11-20, 1984), the promoters of the bacteriophages of *Bacillus* (Gryczan, In: *The Molecular Biology of the Bacilli*, Academic Press, Inc., NY, 1982), and *Streptomyces* promoters (Ward *et al.*, *Mol. Gen. Genet.* 203:468-478, 1986). Prokaryotic promoters are reviewed by Glick (*Ind. Microbiot.* 1:277-282, 1987), Cenatiempo (*Biochimie* 68:505-516, 1986), and Gottesman (*Ann. Rev. Genet.* 18:415-442, 1984).

Proper expression in a prokaryotic cell also requires the presence of a ribosome-binding site upstream of the gene

sequence-encoding sequence. Such ribosome-binding sites are disclosed, for example, by Gold et al. (Ann. Rev. Microbiol. 35:365-404, 1981). The selection of control sequences, expression vectors, transformation methods, and the like, are dependent on the type of host cell used to express the gene. As used herein, "cell", "cell line", and "cell culture" may be used interchangeably and all such designations include progeny. Thus, the words "transformants" or "transformed cells" include the primary subject cell and cultures derived therefrom, without regard to the number of transfers. It is also understood that all progeny may not be precisely identical in DNA content, due to deliberate or inadvertent mutations. However, as defined, mutant progeny have the same functionality as that of the originally transformed cell.

Host cells which may be used in the expression systems of the present invention are not strictly limited, provided that they are suitable for use in the expression of the kinase polypeptide of interest. Suitable hosts may often include eukaryotic cells. Preferred eukaryotic hosts include, for example, yeast, fungi, insect cells, mammalian cells either *in vivo*, or in tissue culture. Mammalian cells which may be useful as hosts include HeLa cells, cells of fibroblast origin such as VERO or CHO-K1, or cells of lymphoid origin and their derivatives. Preferred mammalian host cells include SP2/0 and J558L, as well as neuroblastoma cell lines such as IMR 332, which may provide better capacities for correct post-translational processing.

In addition, plant cells are also available as hosts, and control sequences compatible with plant cells are available, such as the cauliflower mosaic virus 35S and 19S, and nopaline synthase promoter and polyadenylation signal sequences. Another preferred host is an insect cell, for

example the *Drosophila* larvae. Using insect cells as hosts, the *Drosophila* alcohol dehydrogenase promoter can be used (Rubin, Science 240:1453-1459, 1988). Alternatively, baculovirus vectors can be engineered to express large amounts of kinases of the invention in insect cells (Jasny, Science 238:1653, 1987; Miller et al., In: Genetic Engineering, Vol. 8, Plenum, Setlow et al., eds., pp. 277-297, 1986).

Any of a series of yeast expression systems can be utilized which incorporate promoter and termination elements from the actively expressed sequences coding for glycolytic enzymes that are produced in large quantities when yeast are grown in mediums rich in glucose. Known glycolytic gene sequences can also provide very efficient transcriptional control signals. Yeast provides substantial advantages in that it can also carry out post-translational modifications.

A number of recombinant DNA strategies exist utilizing strong promoter sequences and high copy number plasmids which can be utilized for production of the desired proteins in yeast. Yeast recognizes leader sequences on cloned mammalian genes and secretes peptides bearing leader sequences (i.e., pre-peptides). Several possible vector systems are available for the expression of kinases of the invention in a mammalian host.

A wide variety of transcriptional and translational regulatory sequences may be employed, depending upon the nature of the host. The transcriptional and translational regulatory signals may be derived from viral sources, such as adenovirus, bovine papilloma virus, cytomegalovirus, simian virus, or the like, where the regulatory signals are associated with a particular gene sequence which has a high level of expression. Alternatively, promoters from mammalian expression products, such as actin, collagen,

myosin, and the like, may be employed. Transcriptional initiation regulatory signals may be selected which allow for repression or activation, so that expression of the gene sequences can be modulated. Of interest are regulatory  
5 signals which are temperature-sensitive so that by varying the temperature, expression can be repressed or initiated, or are subject to chemical (such as metabolite) regulation.

Expression of kinases of the invention in eukaryotic hosts requires the use of eukaryotic regulatory regions.  
10 Such regions will, in general, include a promoter region sufficient to direct the initiation of RNA synthesis. Preferred eukaryotic promoters include, for example, the promoter of the mouse metallothionein I gene sequence (Hamer et al., J. Mol. Appl. Gen. 1:273-288, 1982); the TK promoter  
15 of Herpes virus (McKnight, Cell 31:355-365, 1982); the SV40 early promoter (Benoist et al., Nature (London) 290:304-31, 1981); and the yeast gal4 gene sequence promoter (Johnston et al., Proc. Natl. Acad. Sci. (USA) 79:6971-6975, 1982; Silver et al., Proc. Natl. Acad. Sci. (USA) 81:5951-5955,  
20 1984).

Translation of eukaryotic mRNA is initiated at the codon which encodes the first methionine. For this reason, it is preferable to ensure that the linkage between a eukaryotic promoter and a DNA sequence which encodes a  
25 kinase of the invention (or a functional derivative thereof) does not contain any intervening codons which are capable of encoding a methionine (i.e., AUG). The presence of such codons results either in the formation of a fusion protein (if the AUG codon is in the same reading frame as the kinase  
30 of the invention coding sequence) or a frame-shift mutation (if the AUG codon is not in the same reading frame as the kinase of the invention coding sequence).

A nucleic acid molecule encoding a kinase of the invention and an operably linked promoter may be introduced into a recipient prokaryotic or eukaryotic cell either as a nonreplicating DNA or RNA molecule, which may either be a linear molecule or, more preferably, a closed covalent circular molecule. Since such molecules are incapable of autonomous replication, the expression of the gene may occur through the transient expression of the introduced sequence.

Alternatively, permanent expression may occur through the integration of the introduced DNA sequence into the host chromosome.

A vector may be employed which is capable of integrating the desired gene sequences into the host cell chromosome. Cells which have stably integrated the introduced DNA into their chromosomes can be selected by also introducing one or more markers which allow for selection of host cells which contain the expression vector.

The marker may provide for prototrophy to an auxotrophic host, biocide resistance, e.g., antibiotics, or heavy metals, such as copper, or the like. The selectable marker gene sequence can either be directly linked to the DNA gene sequences to be expressed, or introduced into the same cell by co-transfection. Additional elements may also be needed for optimal synthesis of mRNA. These elements may include splice signals, as well as transcription promoters, enhancers, and termination signals. cDNA expression vectors incorporating such elements include those described by Okayama (Mol. Cell. Biol. 3:280-, 1983).

The introduced nucleic acid molecule can be incorporated into a plasmid or viral vector capable of autonomous replication in the recipient host. Any of a wide variety of vectors may be employed for this purpose. Factors of importance in selecting a particular plasmid or



viral vector include: the ease with which recipient cells that contain the vector may be recognized and selected from those recipient cells which do not contain the vector; the number of copies of the vector which are desired in a particular host; and whether it is desirable to be able to "shuttle" the vector between host cells of different species.

Preferred prokaryotic vectors include plasmids such as those capable of replication in *E. coli* (such as, for example, pBR322, ColE1, pSC101, pACYC 184,  $\pi$ VX; "Molecular Cloning: A Laboratory Manual", 1989, supra). *Bacillus* plasmids include pC194, pC221, pT127, and the like (Gryczan, In: The Molecular Biology of the Bacilli, Academic Press, NY, pp. 307-329, 1982). Suitable *Streptomyces* plasmids include p1J101 (Kendall et al., *J. Bacteriol.* 169:4177-4183, 1987), and streptomyces bacteriophages such as  $\phi$ C31 (Chater et al., In: Sixth International Symposium on Actinomycetales Biology, Akademiai Kiado, Budapest, Hungary, pp. 45-54, 1986). *Pseudomonas* plasmids are reviewed by John et al. (*Rev. Infect. Dis.* 8:693-704, 1986), and Izaki (*Jpn. J. Bacteriol.* 33:729-742, 1978).

Preferred eukaryotic plasmids include, for example, BPV, vaccinia, SV40, 2-micron circle, and the like, or their derivatives. Such plasmids are well known in the art (Botstein et al., Miami Wntr. Symp. 19:265-274, 1982; Broach, In: "The Molecular Biology of the Yeast *Saccharomyces*: Life Cycle and Inheritance", Cold Spring Harbor Laboratory, Cold Spring Harbor, NY, p. 445-470, 1981; Broach, *Cell* 28:203-204, 1982; Bollon et al., *J. Clin. Hematol. Oncol.* 10:39-48, 1980; Maniatis, In: *Cell Biology: A Comprehensive Treatise*, Vol. 3, Gene Sequence Expression, Academic Press, NY, pp. 563-608, 1980).

Once the vector or nucleic acid molecule containing the construct(s) has been prepared for expression, the DNA construct(s) may be introduced into an appropriate host cell by any of a variety of suitable means, i.e., transformation, transfection, conjugation, protoplast fusion, electroporation, particle gun technology, calcium phosphate-precipitation, direct microinjection, and the like. After the introduction of the vector, recipient cells are grown in a selective medium, which selects for the growth of vector-containing cells. Expression of the cloned gene(s) results in the production of a kinase of the invention, or fragments thereof. This can take place in the transformed cells as such, or following the induction of these cells to differentiate (for example, by administration of bromodeoxyuracil to neuroblastoma cells or the like). A variety of incubation conditions can be used to form the peptide of the present invention. The most preferred conditions are those which mimic physiological conditions.

#### IV. The Proteins of the Invention

A variety of methodologies known in the art can be utilized to obtain the polypeptides of the present invention. The polypeptides may be purified from tissues or cells that naturally produce the polypeptides.

Alternatively, the above-described isolated nucleic acid fragments could be used to express the kinases of the invention in any organism. The samples of the present invention include cells, protein extracts or membrane extracts of cells, or biological fluids. The samples will vary based on the assay format, the detection method, and the nature of the tissues, cells or extracts used as the sample.

Any eukaryotic organism can be used as a source for the polypeptides of the invention, as long as the source organism naturally contains such polypeptides. As used herein, "source organism" refers to the original organism from which the amino acid sequence of the subunit is derived, regardless of the organism the subunit is expressed in and ultimately isolated from.

One skilled in the art can readily follow known methods for isolating proteins in order to obtain the polypeptides free of natural contaminants. These include, but are not limited to: size-exclusion chromatography, HPLC, ion-exchange chromatography, and immuno-affinity chromatography.

#### Mammalian STLK2

Analysis of the deduced amino acid sequence predicts STLK2 to be an intracellular serine/threonine kinase, lacking both a signal sequence and transmembrane domain. STLK2 contains a 21 amino acid N-terminal domain, a 253 amino acid catalytic domain with all the motifs characteristic of a serine/threonine kinase, followed by a 142 amino acid C-terminal domain.

STLK2 is most closely related to human STE20-subfamily kinases, MST3 (GB:AF024636) and SOK-1 (GB:X99325) and a *C. elegans* kinase yk34b11.5 (GB:U53153) sharing 72.7%, 68.7%, and 69.3% amino acid identity, respectively.

The 21 amino acid N-terminal domain of human STLK2 is 71.4% identical to the N-terminus of MST3 (GB:AF024636). Human STLK2 lacks a glycine residue at position 2, and is therefore unlikely to undergo myristylation. A Smith-Waterman search of the nonredundant protein database does not reveal any significant homologies that might suggest a potential function for this domain.

The 253 amino acid catalytic domain of human STLK2 is most related to human SOK-1 (X99325), MST3 (GB:AF024636), *C. elegans* yk32b11.5 (GB:U53153), and STLK3 (SEQ ID NO:6) sharing 88.9%, 87.4%, 78.3%, and 49% amino identity respectively, placing it in the STLK-subfamily of STE20-related kinases. The STLK2 kinase domain displayed lesser homology to other STE20-related kinases including: 55.9% to human MST2 (GB:U26424), 49.2% to human GCK (GB:U07349), 49.2% to human KHS1 (GB:U77129), and 44.2% to human HPK1 (GB:U66464). The activation loop of human STLK2 catalytic domain is identical to that of human SOK-1 and MST3 including the presence of four potential threonine phosphorylation sites that could serve an autoregulatory role on kinase activity.

The 142 amino acid C-terminal domain of human STLK2 is most related to human SOK-1 (X99325), MST3 (GB:AF024636), and *C. elegans* yk32b11.5 (GB:U53153), sharing 39.9%, 39.9%, and 33.3% amino acid identity, respectively. This C-terminal domain shares some significant amino acid similarity to the C-terminal domains of the related human STLK3 (SEQ ID NO:6) and STLK4 (SEQ ID NO:7).

The C-terminus of the related human SOK-1 (GB:X99325) kinase has been shown to be inhibitory to the catalytic activity of this kinase (Pombo, C.M., Bonventre, J.V., Molnar, A., Kyriakis, J. and Force, T. EMBO J. 15, 4537-4546 (1996)). Based on the sequence identity between the C-termini of human SOK-1 (GB:X99325) and human STLK2 (39.2%), the C-terminus of human STLK2 may also function as an inhibitory domain for its kinase.

#### Mammalian STLK3

The 3030 bp human STLK3 nucleotide sequence of the partial cDNA clone encodes a polypeptide of 516 amino acids

(SEQ ID NO:6) with a predicted molecular mass of 56,784 daltons. Analysis of the deduced amino acid sequence predicts STLK3 to be an intracellular serine/threonine kinase, lacking both a signal sequence and transmembrane domain, however the cDNA clone lacks an initiating ATG, so the full extent of its N-terminus is not known. STLK3 contains a 31 amino acid N-terminal domain, a 277 amino acid catalytic domain with all the motifs characteristic of a serine/threonine kinase, followed by a 181 amino acid C-terminal domain containing a 25 amino acid insert and a 27 amino acid tail relative to the sequence of human STLK2.

STLK3 is most closely related to human STE20-subfamily kinases, STLK4 (SEQ ID NO:7), MST3 (GB:AF024636), SOK-1 (GB:X99325) and STLK2 (SEQ ID NO:5) sharing 71.1%, 37.6%, 38.1%, and 38.4% amino acid identity respectively.

The 31 amino acid N-terminal domain of human STLK3 lacked any significant amino acid sequence homologies using a Smith-Waterman search of the nonredundant protein database, other than sequence similarity to proline-alanine repeats.

The 277 amino acid catalytic domain of human STLK3 is most related to human STLK4 (SEQ ID NO:7), SOK-1 (GB:X99325), MST3 (GB:AF024636), and STLK2 (SEQ ID NO:5) sharing 88.2%, 49.2%, 49%, and 49% amino acid identity, respectively. It also shares strong homology to other STKs from lower organisms including 51.7% to *A. thaliana* (GB:AC002343), 43.1% to *A. thaliana* (GB:Z97336), 42.1% to *A. thaliana* (GB:U96613), and 43.3% to *C. elegans* (GB:U53153).

The activation loop of the human STLK3 catalytic domain conserves three potential threonine phosphorylation sites with other members of the STLK-subfamily of STE20-related kinases (human STE20, MST3, STLK2, STLK4) that could serve an autoregulatory role on kinase activity.

The 181 amino acid C-terminal domain of human STLK3 shares 55.5% amino acid identity to human STLK4 (SEQ ID NO:7), and is 100% identical to a partial human cDNA DCHT (GB:AF017635). The C-terminal domain of human STLK3  
5 contains a 26 amino acid insert relative to human STE20. A similar (87.5% amino acid identity) 26 amino acid insert is also present in human STLK4.

The 27 amino acid C-terminal tail of human STLK3 shares 77.8% amino acid identity to human STLK4, but is absent from  
10 other STLK-family members. This high degree of homology between the C-tail of two STLK-family members suggests they may be involved in an as yet unidentified protein-protein interaction.

The weak sequence homology between the C-termini of  
15 human STLK3 and STE20, suggests it may also function as an inhibitory domain for its kinase.

#### Mammalian STLK4

The 3857 bp human STLK4 nucleotide sequence of the  
20 partial cDNA clone encodes a polypeptide of 414 amino acids (SEQ ID NO:7) with a predicted molecular mass of 45,451 daltons. Analysis of the deduced amino acid sequence predicts STLK4 to be an intracellular serine/threonine kinase, lacking both a signal sequence and transmembrane  
25 domain, however the cDNA clone lacks an initiating ATG, so the full extent of its N-terminus is not known. The partial STLK4 protein sequence contains a 178 amino acid catalytic domain corresponding to the C-terminal motifs VI-XI of a serine/threonine kinase, followed by a 236 amino acid C-  
30 terminal domain containing two inserts of 25 and 41 amino acids each, relative to the sequence of human STLK2.

STLK4 is most closely related to human STE20-subfamily kinases, STLK3 (SEQ ID. NO 6), MST3 (GB:AF024636), STLK2

(SEQ ID NO:5), and SOK-1 (GB:X99325) sharing 71.0%, 46.8%, 43.9%, and 37.7% amino acid identity, respectively.

The 178 amino acid catalytic domain of human STLK4 is most related to human STLK3 (SEQ ID NO. 7), SOK-1 (GB:X99325), MST3 (GB:AF024636), STLK2 (SEQ ID NO:5), and MST1 (GB:U18297), sharing 88.2%, 54.2%, 54.0%, 53.7 and 45.7% amino acid identity, respectively. It also shares strong homology to other STKs from lower organisms including 56.9% to *A. thaliana* (GB: AC002343), 52.5% to *C. elegans* (GB: U53153), 46.2% to *A. thaliana* (GB: Z97336) and 45.7% to *A. thaliana* (GB: U96613). The activation loop of the human STLK4 catalytic domain conserves three potential threonine phosphorylation sites with other members of the STLK-subfamily of STE20-related kinases (human STE20, MST3, STLK2 and STLK3) that could serve an autoregulatory role on kinase activity.

The 236 amino acid C-terminal domain of human STLK4 shares 58.1% amino acid identity to both human STLK3 (SEQ ID NO:6) and to a partial human cDNA, DCHT (GB:AF017635). The C-terminal domain of human STLK4 contains a 25 amino acid insert relative to human SOK-1 and shares 87.5% amino acid identity to an insert present in human STLK3.

The weak sequence homology between the C-termini of human STLK4 and STE20, suggests it may also function as an inhibitory domain for its kinase.

#### Mammalian STLK5

The full-length 2110 bp human STLK5 cDNA encodes a polypeptide of 373 amino acids (SEQ ID NO:97) with a predicted molecular mass of 41,700 daltons. Analysis of the deduced amino acid sequence predicts STLK5 to be an intracellular STE20-subfamily kinase, lacking both a signal sequence and transmembrane domain. STLK5 contains a 10

amino acid N-terminal domain, a 311 amino acid catalytic domain with all the motifs characteristic of a serine/threonine kinase, and a 52 amino acid C-terminal domain.

5           STLK5 is most closely related to the human STE20-subfamily kinases STLK6 (SEQ ID No. 99) and SPAK (AF099989), sharing 51% and 33% amino acid identity, respectively, over its full extent. It also shares significant homology to database entries from *Arabidopsis thaliana* (GB:AC002343) and  
10       *C.elegans* (GB:AL023843, GB:AL023843).

          The 10 amino acid N-terminal domain of human STLK5 does not reveal any significant homologies to the protein database.

          The 311 amino acid catalytic domain of human STLK5  
15       shares 51% and 34 % identity to STLK6 and SPAK, respectively. The catalytic domain of STLK5 contains a 45 amino acid insert between kinase subdomains X and XI relative to human STE20. Multiple human EST fragments as well as a murine EST (GB:AA575647) contain this insert  
20       providing evidence that this region is an integral part of STLK5.

          The 52 amino acid C-terminal tail of human STLK5 shares 41.3% amino acid identity to human SOK-1 (GB:X99325). The weak sequence homology between the C-termini of human STLK5  
25       and STE20, suggests it may also function as an inhibitory domain for its kinase.

#### Mammalian STLK6

          The 2,001 bp human STLK6 nucleotide sequence of the  
30       complete cDNA encodes a polypeptide of 418 amino acids (SEQ ID NO:99) with a predicted molecular mass of 47,025 daltons. Analysis of the deduced amino acid sequence predicts STLK6 to be an intracellular STE20-subfamily kinase, lacking both



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a signal sequence and transmembrane domain. STLK6 contains a 57 amino acid N-terminal domain, a 312 amino acid catalytic domain with all the motifs characteristic of a serine/threonine kinase, followed by a 49 amino acid C-terminal domain.

STLK6 is most closely related to human STE20-subfamily kinases STLK5 (SEQ ID NO:97), STLK7 (SEQ ID NO:101), and SPAK (AF099989), sharing 50%, 35%, and 30% amino acid identity over its full extent. It also shares significant homology to database entries from *Arabidopsis thaliana* (GB:AC002343) and *C.elegans* (GB:U53153).

The 57 amino acid N-terminal domain of human STLK6 does not reveal any significant homologies in the protein database.

The 312 amino acid catalytic domain of human STLK6 shares 51 and 30 % identity to human STLK5 and SPAK, respectively.

The 49 amino acid C-terminal tail of human STLK6 shares low amino acid sequence identity (29%) with STLK5 and SPAK.

#### Mammalian STLK7

The 311 bp human STLK7 nucleotide sequence of the partial cDNA encodes a polypeptide of 103 amino acids (SEQ ID NO:101). Analysis of the deduced amino acid sequence predicts STLK7 to be an internal fragment of an intracellular STE20-family kinase. This sequence lacks the N- and C-terminal portions of STLK7 and contains only the N-terminal 103 amino acids of the predicted catalytic domain.

Human STLK7 is most closely related to human STE20-subfamily kinases SPAK (AF099989), STLK5 (SEQ ID NO:97), and STLK6 (SEQ ID NO:99), sharing 86%, 38%, and 35% amino acid identity within this region of the kinase domain. It also

shares significant homology to database entries from *Arabidopsis thaliana* (GB:AC002343) and *Drosophila melanogaster* (GB:AF006640).

5     Mammalian ZC1

      The 3798 bp human ZC1 nucleotide sequence encodes a polypeptide of 1239 amino acids (SEQ ID NO:13) with a predicted molecular mass of 142,140 daltons. Analysis of the deduced amino acid sequence predicts ZC1 to be an  
10    intracellular serine/threonine kinase, lacking both a signal sequence and transmembrane domain. The full-length ZC1 protein contains a 22 amino acid N-terminus, a 267 amino acid catalytic domain with all the motifs characteristic of a serine/threonine kinase, a 237 amino acid region predicted  
15    to form a coiled-coil structure, a 114 amino acid proline-rich region, a 256 amino acid spacer region, followed by a 343 amino acid C-terminal domain containing a potential Rab/Rho-binding region.

      ZC1 is most closely related to the human STE20-subfamily kinases ZC2 (SEQ ID NO:14), ZC3 (SEQ ID NO:15),  
20    and ZC4 (SEQ ID NO:16), sharing 61.7%, 60.9%, and 43.8% amino acid identity, respectively. ZC1 also shares 45.5% amino acid identity to a *C. elegans* kinase encoded by the cosmid ZC504.4 (GB:Z50029). ZC1 exhibits 90.0% amino acid  
25    homology to murine NIK (GB:U88984), suggesting it may be the human orthologue of this STK.

      The 22 amino acid N-terminal domain of human ZC1 is 58.8% identical to the *C. elegans* kinase encoded by the cosmid ZC504.4 (GB:Z50029), and 100% identical to murine NIK  
30    (GB: U88984). Human ZC1 lacks a glycine residue at position 2, and is therefore unlikely to undergo myristylation. A Smith-Waterman search of the nonredundant protein database

does not reveal any significant homologies that might suggest a potential function for this domain.

The 267 amino acid catalytic domain of human ZC1 is most related to human STE20-subfamily kinases, ZC3 (SEQ ID NO:15), ZC2 (SEQ ID NO:14), KHS2 (SEQ ID NO:18), SOK-1 (GB:X99325), GCK (GB:U07349), and GEK2 (SEQ ID NO:107), and to the *C. elegans* kinase encoded by the cosmid ZC504.4 (GB:Z50029) sharing 90.6%, 90.2%, 50.6%, 47.4%, 45.4%, 42.5% and 82.6% amino acid identity, respectively. The ZC1 kinase domain shares 98.1% identity to murine NIK (GB:U88984). ZC1 contains the potential "TPY" regulatory phosphorylation site in its activation loop. This "TPY" motif is conserved in other STE20-related kinases, including ZC2, ZC3, ZC4, GEK2, KHS2, SULU1, SULU3, PAK4 and PAK5.

Immediately C-terminal to the kinase domain of human ZC1 is a 237 amino acid region predicted to form a coiled-coil structure based on the Lupas algorithm (Lupas, A. Meth. Enzymol. 266, 513-525 (1996)). This region of ZC1 is most related to human STE20-subfamily kinases, ZC3 (SEQ ID NO:15), ZC2 (SEQ ID NO:14), and GEK2 (SEQ ID NO:107), as well as to human PITSLRE (GB:U04824) sharing 65.5%, 65.4%, 25.3%, and 29.0% amino acid identity, respectively. The ZC1 coiled-coil domain also shares 90.6% amino acid homology to murine NIK. The *C. elegans* homologue ZC504.4 shares 32.2% sequence identity over this region.

Within the predicted coiled-coil domain of human ZC1, and the related ZC3, is a region predicted to form a leucine zipper (Leu-X6-Leu-X6-Leu-X6-Leu-X20-Leu-X6-Leu). The fact that this leucine repeat exists within a predicted coiled-coil structure suggests that the leucine zipper may have a high probability of serving as a dimerization interface (Hirst, J.D. et al Protein Engineering 9 657-662 (1996))

mediating a potential inter- or intra-molecular dimerization of human ZC1.

The 114 amino acid proline-rich region of human ZC1 is most related to human STE20-subfamily kinases, ZC2 (SEQ ID NO:14) and ZC3 (SEQ ID NO:15), sharing 35.8%, and 24.9%, respectively. The ZC1 proline-rich domain shares 36.4% amino acid homology to murine NIK (GB:U88984). Three potential "PxxP" SH3 domain-binding motifs (I, II and III) are found within the proline-rich region of human ZC1. Motif I is conserved in human ZC1 and *C. elegans* ZC504.4 (GB:Z50029). Motif II is conserved in ZC1, ZC2, ZC3, ZC4 and *C. elegans* ZC504.4. Motif III is conserved in ZC1, ZC2, ZC3 and ZC4. Motifs II and III of murine NIK have been shown to bind the SH3 motif of the adaptor molecule Nck (Su, Y-C. *et al*, EMBO J. 16, 1279-1290 (1997)). From this evidence, human ZC1 may have the potential to bind to Nck or other SH3 or WW domain-containing proteins and participate in growth factor-induced signaling pathways.

The 256 amino acid spacer region of human ZC1 is most related to human STE20-subfamily kinases, ZC2 (SEQ ID NO:14) and ZC3 (SEQ ID NO:15), as well as to human PITSLRE (GB:U04824), sharing 59.9%, 33.1%, 29.6%, and 26.4% amino acid identity, respectively. It also shares 59.9% amino acid homology to murine NIK. The *C. elegans* homologue ZC504.4 has only limited sequence similarity in this spacer region.

The 343 amino acid C-terminal of human ZC1 is most related to human STE20-subfamily kinases, ZC3 (SEQ ID NO:15), ZC2 (SEQ ID NO:14), and ZC4 (SEQ ID NO:16), sharing 89.2%, 88.9%, and 42.3%, amino acid identity, respectively.

The ZC1 C-terminal domain also shares 98.8% amino acid identity to murine NIK. The *C. elegans* homologue ZC504.4 also shares 68.7% amino acid identity with the C-tail of

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human ZC1. A lower, yet significant, homology is also evident to human KHS2 (SEQ ID NO:18), GCK (GB:U07349), and murine citron (GB:U07349) with 26.6%, 23.1% and 36.2% amino acid identity, respectively. GCK is a STE20-family kinase whose C-terminal domain has been shown to bind the small G-protein Rab8 (Ren, M. *et al.*, Proc. Natl. Acad. Sci. 93, 5151-5155 (1996)). Citron is a non-kinase Rho-binding protein (Madaule, P. *et al.*, FEBS Lett. 377, 243-238 (1995)).

10 The sequence similarity of the C-terminal region of ZC1 to proteins that have potential Rab- or Rho-binding domains suggests that ZC1 may signal through a small G-protein-dependant pathway.

15 Mammalian ZC2

The 4055 bp human ZC2 nucleotide sequence of the partial cDNA encodes a polypeptide of 1297 amino acids (SEQ ID NO:14) with a predicted molecular mass of 147,785 daltons. Analysis of the deduced amino acid sequence predicts ZC2 to be an intracellular serine/threonine kinase, lacking both a signal sequence and transmembrane domain, however the cDNA clone lacks an initiating ATG, so the full extent of its N-terminus is not known. The N-terminally truncated ZC2 protein contains a 255 amino acid catalytic domain with all the motifs characteristic of a serine/threonine kinase, a 187 amino acid region predicted to form a coiled-coil structure, a 184 amino acid proline-rich region, a 328 amino acid spacer region, followed by a 343 amino acid C-terminal domain containing a potential Rab/Rho-binding region.

30 ZC2 is most closely related to the human STE20-subfamily kinases ZC3 (SEQ ID NO:15), ZC1 (SEQ ID NO:13), and ZC4 (SEQ ID NO:16), sharing 88.3%, 61.7%, and 41.9%

amino acid identity, respectively, and shares 41.7% amino acid identity to a *C. elegans* kinase encoded by the cosmid ZC504.4 (GB:Z50029).

5 The 255 amino acid catalytic domain of human ZC2 is most related to human STE20-subfamily kinases, ZC1 (SEQ ID NO:13), ZC3 (SEQ ID NO:15), SOK-1 (GB:X99325), KHS2 (SEQ ID NO:18), MST1 (GB:U18297), and GCK (GB:U07349), and to the *C. elegans* kinase encoded by the cosmid ZC504.4 (GB:Z50029) sharing 90.2%, 89.8%, 49.0%, 48.6%, 47.9%, 45.0 and 76.7% amino acid identity, respectively. ZC2 contains the potential "TPY" regulatory phosphorylation site in its activation loop. This "TPY" motif is conserved in other STE20-related kinases, including ZC1, ZC3, ZC4, GEK2, KHS2, SULU1, SULU3, PAK4 and PAK5.

10 Immediately C-terminal to the kinase domain of human ZC2 is a 187 amino acid region predicted to form a coiled-coil structure based on the Lupas algorithm (supra). This region of ZC2 is most related to human STE20-subfamily kinases, ZC1 (SEQ ID NO:13), ZC3 (SEQ ID NO:15), and GEK2 (SEQ ID NO:107), as well as to human PITSLRE (GB:U04824), sharing 65.8%, 61.5%, 29.7% and 29.6% amino acid identity, respectively. The *C. elegans* homologue ZC504.4 shares 30.8% sequence identity over this region. Human ZC2 lacks the potential leucine zipper found in ZC1 as a consequence of a 25 29 amino acid deletion relative to ZC1 and ZC3.

30 The 184 amino acid proline-rich region of human ZC2 is most related to human STE20-subfamily kinases, ZC3 (SEQ ID NO:15) and ZC1 (SEQ ID NO:13), sharing 35.9% and 28.6%, amino acid identity, respectively. Significant homology is also evident to the murine WW domain-binding protein WBP7 (GB:U92455), and to the human SH3 domain-binding protein 3BP-1 (GB:X87671), with 27.7% and 25.3% amino acid identity, respectively.

ZC2 contains two of the potential "PxxP" SH3 domain-binding motifs (II and III) found within the proline-rich region of human ZC1. Motif II is conserved in ZC1, ZC3, ZC4 and *C. elegans* ZC504.4, and Motif III is conserved in ZC1, ZC3 and ZC4. Motifs II and III of murine NIK have been shown to bind the SH3 motif of the adaptor molecule Nck. From this evidence, human ZC1 may have the potential to bind to Nck or other SH3 or WW domain-containing proteins, and to participate in growth factor-induced signaling pathways.

The 328 amino acid spacer region of human ZC2 is most related to human STE20-subfamily kinases ZC1 (SEQ ID NO:13) and ZC3 (SEQ ID NO:15), and to murine NIK (GB:U88984), sharing 31.6%, 26.9% and 25.9% amino acid identity, respectively. The *C. elegans* homologue ZC504.4 has only limited sequence similarity in this spacer region.

The 343 amino acid C-terminal of human ZC2 is most related to human STE20-subfamily kinases ZC1 (SEQ ID NO:13), ZC3 (SEQ ID NO:15) and ZC4 (SEQ ID NO:16), and to murine NIK (GB:U88984), sharing 88.9%, 88.3%, 41.9%, and 88.0%, amino acid identity, respectively. The *C. elegans* homologue, ZC504.4, also shares 67.2% amino acid identity with the C-tail of human ZC2. A lower, yet significant, homology is also evident to human GCK (GB:U07349), murine citron (GB:U07349), and the *S. cerevisiae* ROM2 protein (GB:U19103), a Rho1 GDP/GTP exchange factor, with 22.3%, 22.2% and 21.9% amino acid identity, respectively.

The sequence similarity of the C-terminal region of ZC2 to proteins that have potential Rab- or Rho-binding domains suggests that ZC2, like ZC1, may also signal through a small G-protein-dependant pathway.

Mammalian ZC3

The 4133 bp human ZC3 nucleotide sequence of the partial cDNA encodes a polypeptide of 1326 amino acids (SEQ ID NO:15) with a predicted molecular mass of 149,906 daltons. Analysis of the deduced amino acid sequence predicts ZC3 to be an intracellular serine/threonine kinase, lacking both a signal sequence and transmembrane domain, however the cDNA clone lacks an initiating ATG, so the full extent of its N-terminus is not known. The N-terminally truncated ZC3 protein contains a 255 amino acid catalytic domain with all the motifs characteristic of a serine/threonine kinase: a 221 amino acid region predicted to form a coiled-coil structure, a 204 amino acid proline-rich region, and a 303 amino acid spacer region followed by a 343 amino acid C-terminal domain containing a potential Rab/Rho-binding region.

ZC3 is most closely related to the human STE20-subfamily kinases ZC1 (SEQ ID NO:13), ZC2 (SEQ ID NO:14), and ZC4 (SEQ ID NO:16), sharing 62.0%, 61.0%, and 42.5% amino acid identity, respectively and shares 46.7% amino acid identity to a *C. elegans* kinase encoded by the cosmid ZC504.4 (GB:Z50029).

The 255 amino acid catalytic domain of human ZC3 is most related to human STE20-subfamily kinases, ZC1 (SEQ ID NO:13), ZC2 (SEQ ID NO:14), SOK-1 (GB:X99325), KHS2 (SEQ ID NO:18), GCK (GB:U07349), SULU1 (SEQ ID NO:22), and GEK2 (SEQ ID NO:107), and to the *C. elegans* kinase encoded by the cosmid ZC504.4 (GB:Z50029) sharing 90.6%, 89.3%, 49.0%, 48.3%, 45.0%, 43.1%, 42.3% and 76.7% amino acid identity, respectively. ZC1 contains the potential "TPY" regulatory phosphorylation site in its activation loop. This "TPY" motif is conserved in other STE20-related kinases, including ZC1, ZC2, GEK2, KHS2, SULU1, SULU3, PAK4 and PAK5.



Immediately C-terminal to the kinase domain of human ZC3 is a 221 amino acid region predicted to form a coiled-coil structure based on the Lupas algorithm (supra). This region of ZC3 is most homologous to human STE20-subfamily kinases, ZC1 (SEQ ID NO:13), ZC2 (SEQ ID NO:14), and GEK2 (SEQ ID NO:107), sharing 66.9%, 61.5%, and 27.5% identity, as well as to rat PLC-beta (GB:A45493) and human PITSLRE (GB:H54024) sharing 29.6% and 25.9% amino acid identity, respectively. The *C. elegans* homologue ZC504.4 shares 26.8% sequence identity over this region.

Within the predicted coiled-coil domain of human ZC3, and the related ZC1, is a region predicted to form a leucine zipper (Leu-X6-Leu-X6-Leu-X6-Leu-X20-Leu-X6-Leu). The fact that this leucine repeat exists within a predicted coiled-coil structure suggests that the leucine zipper may have a high probability of serving as a dimerization interface (Hirst, J.D. et al Protein Engineering 9 657-662 (1996)) mediating a potential inter- or intra-molecular dimerization of human ZC3.

The 204 amino acid proline-rich region of human ZC3 is most related to human STE20-subfamily kinases, ZC1 (SEQ ID NO:13) and ZC2 (SEQ ID NO:14), sharing 66.9% and 61.5% amino acid identity, respectively.

ZC3 contains two of the potential "PxxP" SH3 domain-binding motifs (II and III) found within the proline-rich region of human ZC1. Motif II is conserved in ZC1, ZC2, ZC4 and *C. elegans* ZC504.4; Motif III is conserved in ZC1, ZC2 and ZC4. Motifs II and III of murine NIK have been shown to bind the SH3 motif of the adaptor molecule Nck. From this evidence, human ZC3 may have the potential to bind to Nck or other SH3 or WW domain-containing proteins and participate in growth factor-induced signaling pathways.

The 303 amino acid spacer region of human ZC3 is most related to human STE20-subfamily kinases, ZC1 (SEQ ID NO:13) and ZC2 (SEQ ID NO:14) sharing 30.1%, and 27.1% amino acid identity, respectively. The *C. elegans* homologue ZC504.4 lacks nearly the entire spacer region of ZC3.

The 343 amino acid C-terminal of human ZC3 is most related to human STE20-subfamily kinases, ZC1 (SEQ ID NO:13), ZC2 (SEQ ID NO:14) and ZC4 (SEQ ID NO:16), sharing 89.2%, 88.9%, and 42.5%, amino acid identity, respectively. The *C. elegans* homologue ZC504.4 also shares 67.2% amino acid identity with the C-tail of human ZC3. A lower, yet significant, homology is also evident to human GCK (GB:U07349), as well as to the non-kinases murine citron (GB:U07349) and the *S. cerevisiae* ROM2 protein (GB:U19103), a Rho1 GDP/GTP exchange factor, with 21.6%, 32.4% and 22.9% amino acid identity, respectively.

The sequence similarity of the C-terminal region of ZC3 to proteins that have potential Rab- or Rho-binding domains suggests that ZC3, like ZC1 and ZC2, may signal through a small G-protein-dependant pathway.

#### Mammalian ZC4

The 3,684 bp human ZC4 nucleotide sequence of the complete cDNA encodes a polypeptide of 1,227 amino acids (SEQ ID NO:105) with a predicted molecular mass of 138,205 Daltons. Analysis of the deduced amino acid sequence predicts ZC4 to be an intracellular STE20-subfamily kinase, lacking both a signal sequence and a transmembrane domain. The full-length ZC4 protein contains a 25 amino acid N-terminus, a 265 amino acid catalytic domain with all the motifs characteristic of a serine/threonine kinase, a 108 amino acid region predicted to form a coiled-coil structure, a 231 amino acid proline-rich region, a 40 amino acid region

predicted to form a coiled-coil structure spacer region, a 204 amino acid spacer region (domain B), followed by a 355 amino acid C-terminal domain containing a potential Rab/Rho-binding region (domain C).

5           ZC4 is most closely related to human ZC1 (SEQ ID NO:13, also known as human HGK, human KIAA0687, murine NIK, human AC005035, human NIK, and *C. elegans* MIG-15), ZC2 (SEQ ID NO:14, similar to partial sequence human KIAA0551), and ZC3 (SEQ ID NO:15). An assembled genomic fragment in the  
10       database (Z83850) is identical to ZC4, except for inappropriate identification of the exon boundaries. (Abo et al. (1998) EMBO J. 17: 6527-6540.)

          The 25 amino acid N-terminal domain of human ZC4 shares weak homology to human ZC1 in its C-terminal extent, but  
15       otherwise does not reveal any significant homologies to the protein database.

          The 265 amino acid catalytic domain of human ZC4 is most related to human ZC1 (SEQ ID NO:13), ZC3 (SEQ ID NO:15), and ZC2 (SEQ ID NO:14), sharing 63%, 64% and 62%  
20       amino acid identity, respectively.

          Immediately C-terminal to the kinase domain of human ZC4 is a 108 amino acid region predicted to form a coiled-coil structure based on the Lupas algorithm (supra). This region is most related to human ZC1 (SEQ ID NO:13), ZC3 (SEQ  
25       ID NO:15), and ZC2 (SEQ ID NO:14), sharing 29%, 25% and 20% amino acid identity, respectively.

          The 231 amino acid proline-rich region of human ZC4 does not reveal any significant homologies to the protein database. This region of ZC4 contains two "PxxP" motifs  
30       that could potentially bind to proteins containing SH3 or WW domains and allow ZC4 to participate in growth factor activated signaling pathways. In addition, within the pro-rich domain of human ZC4 is a region predicted to form a

leucine zipper (Leu-X6-Leu-X6-Leu-X6-Leu-X20-Leu-X6-Leu) which may serve as a dimerization interface. The ZC STE20 subfamily kinases (ZC1, ZC2 and ZC3) have similarly located "PxxP" motifs and potential Leu zippers.

5           Immediately C-terminal to the proline-rich region of human ZC4 is a 40 amino acid region also predicted to form a coiled-coil structure based on the Lupas algorithm. This region of human ZC4 does not reveal any significant homologies to the protein database.

10           The 204 amino acid acidic- and serine-rich domain "B" of ZC4 does not reveal any significant homologies to the protein database.

          The 355 amino acid C-terminal of human ZC4 is most related to human ZC1 (SEQ ID NO:13), ZC3 (SEQ ID NO:15), and  
15           ZC2 (SEQ ID NO:14), sharing 43%, 42% and 42% amino acid identity, respectively.

          The sequence similarity of the C-terminal region of ZC4 to proteins that have potential Rab- or Rho-binding domains suggests that ZC4, like other ZC-subfamily STE20 kinases,  
20           may signal through a small G-protein-dependant pathway.

#### Mammalian KHS2

          The 4023 bp human KHS2 nucleotide sequence encodes a polypeptide of 894 amino acids (SEQ ID NO:18) with a  
25           predicted molecular mass of 101,327 daltons. Analysis of the deduced amino acid sequence predicts KHS2 to be an intracellular serine/threonine kinase, lacking both a signal sequence and transmembrane domain. The full-length KHS2 protein contains a 13 amino acid N-terminus, a 260 amino  
30           acid catalytic domain with all the motifs characteristic of a serine/threonine kinase, a 73 amino acid spacer region, a 188 proline-rich region, followed by a 360 amino acid C-terminal domain containing a potential Rab/Rho-binding site.

KHS2 is most closely related to the human STE20-subfamily kinases KHS1 (GB:U177129), GCK (GB:U07349), and HPK1 (GB:U07349), sharing 65.5%, 51.9%, and 44.9% amino acid identity, respectively and shares 38.5% amino acid identity to a *C. elegans* STK (GB:U55363).

The 13 amino acid N-terminal domain of human KHS2 does not reveal any significant homologies that might suggest a potential function for this domain when examined by a Smith-Waterman alignment to the nonredundant protein database. Human KHS2 lacks a glycine residue at position 2, and is therefore unlikely to undergo myristylation.

The 260 amino acid catalytic domain of human KHS2 is most related to human STE20-subfamily kinases KHS1 (GB:U177129), GCK (GB:U07349), HPK1 (GB:U66464), SOK-1 (GB:X99325), MST1 (GB:U18297), ZC1 (SEQ ID NO:13), and to the *C. elegans* kinase (GB:U55363), sharing 85.4%, 75.1%, 67.7%, 51.4%, 48.1%, 49.8% and 72.0% amino acid identity, respectively. KHS2 contains the potential "TPY" regulatory phosphorylation site in its activation loop. This "TPY" motif is conserved in other STE20-related kinases, including ZC1, ZC2, ZC3, ZC4, GEK2, SULU1, SULU3, PAK4 and PAK5.

The 73 amino acid spacer region of human KHS2 is most related to human STE20-subfamily kinases, KHS1 (GB:U177129), HPK1 (GB:U66464) and GCK (GB:U07349), sharing 60.3%, 43.5% and 44.0%, amino acid identity, respectively.

The 188 amino acid proline-rich region of human KHS2 is most related to human STE20-subfamily kinases, HPK1 (GB:U66464), GCK (GB:U07349) and KHS1 (GB:U177129), sharing 33.3%, 31.9% and 31.4%, amino acid identity, respectively.

Two potential "PxxP" SH3 domain-binding motifs (I and II) are found within the proline-rich region of human KHS2. Motif I is conserved with human KHS1 and HPK1; motif II is

conserved with GCK and KHS2. A 192 amino acid region of human HPK1 containing motif II has been shown to bind to the C-terminal SH3 motif of the adaptor molecule Grb2 (Anafi, M et al, J. Biol. Chem. J. 272, 27804-27811 (1997)). Human  
5 KHS2 may bind SH3 or WW domain-containing proteins through this proline-rich region.

The 360 amino acid C-terminal of human KHS2 is most related to KHS1 (GB:U177129), GCK (GB:U07349) and HPK1 (GB:U66464), and to the *C. elegans* kinase (GB:U55363),  
10 sharing 74.9%, 54.8%, 42.9%, and 31.0%, amino acid identity, respectively. GCK is a STE20-family kinase whose C-terminal domain has been shown to bind the small G-protein Rab8 (Ren, M. et al., Proc. Natl. Acad. Sci. 93, 5151-5155 (1996)).

#### 15 Mammalian SULU1

The 4196 bp human SULU1 nucleotide sequence encodes a polypeptide of 898 amino acids (SEQ ID NO:22) with a predicted molecular mass of 105,402 daltons. Analysis of the deduced amino acid sequence predicts SULU1 to be an  
20 intracellular serine/threonine kinase, lacking both a signal sequence and transmembrane domain. The full-length SULU1 protein contains a 21 amino acid N-terminus, a 256 amino acid catalytic domain with all the motifs characteristic of a serine/threonine kinase, a 150 amino acid spacer region, a  
25 210 amino acid region predicted to form a coiled-coil structure, a 114 amino acid spacer region and a 147 amino acid C-terminal domain predicted to form a coiled-coil structure.

SULU1 is most closely related to the STE20-subfamily  
30 kinases murine SULU3 (SEQ ID NO:24), human SULU3 (SEQ ID NO:23), and to the *C. elegans* kinase SULU (GB:U11280), sharing 68.9%, 72.2% and 38.2% amino acid identity, respectively.

The 21 amino acid N-terminal domain of human SULU1 is most related to murine SULU3 (SEQ ID NO:24) and to the *C. elegans* kinase SULU (GB:U11280), sharing 86.3% and 62.3% amino acid identity. Human SULU1 lacks a glycine residue at position 2, and is therefore unlikely to undergo myristoylation. A Smith-Waterman search of the nonredundant protein database does not reveal any significant homologies that might suggest a potential function for this domain.

The 256 amino acid catalytic domain of human SULU1 is most related to murine SULU3 (SEQ ID NO:24), and to human SOK-1 (GB:X99325), STK2 (SEQ ID NO:5), MST1 (GB:U18297), PAK1 (GB:U24152), ZC2 (SEQ ID NO:14), and KHS2 (SEQ ID NO:18) sharing 86.3%, 48.1%, 46.9%, 45.2%, 43.3%, 43.1% and 42.0% amino acid identity, respectively. The *C. elegans* SULU STK (GB:U11280) shares 62.3% sequence identity over this region. SULU1 contains the potential "TPY" regulatory phosphorylation site in its activation loop. This "TPY" motif is conserved in other STE20-related kinases, including ZC1, ZC2, ZC3, ZC4, GEK2, KHS2, SULU3, PAK4 and PAK5.

The 150 amino acid spacer region of human SULU1 is most related to human SULU3 (SEQ ID NO:23) and to the *C. elegans* kinase (GB:U11280), sharing 53.5% and 10.4% amino acid identity, respectively.

Immediately C-terminal to the spacer region of human SULU1 is a 210 amino acid region predicted to form a coiled-coil structure based on the Lupas algorithm. This region of SULU1 is most related to SULU3 (SEQ ID NO:23), the *C. elegans* SULU kinase (GB:U11280), GEK 2 (SEQ ID NO:107) and ZC1 (SEQ ID NO:13), sharing 68.6%, 26.8%, 23.2%, and 22.8% amino acid identity, respectively.

The 114 amino acid spacer region human SULU1 is most related to human SULU3 (SEQ ID NO:24) with 73.7% amino acid

sequence identity. A lower, yet significant, homology is also evident to murine PITSLRE (GB:U04824) and DLK (GB:A55318), human ZC1 (SEQ ID NO:13) and GEK 2 (SEQ ID NO:107), as well as to the *C. elegans* SULU STK (GB:U11280), sharing 39.7%, 35.4%, 29.5%, 23.6% and 37.6% amino acid identity, respectively.

Immediately C-terminal to the second spacer region of human SULU1 is a 147 amino acid region predicted to form a coiled-coil structure based on the Lupas algorithm. This region of SULU1 is most related to human SULU3 (SEQ ID NO:24), ZC1 (SEQ ID NO:13) and GEK 2 (SEQ ID NO:107), as well as to the *C. elegans* SULU STK (GB:U11280), sharing 73.3%, 28.4%, 26.1% and 39.5%, amino acid identity, respectively.

#### Mammalian (human) SULU3

The 3824 bp partial cDNA human SULU3 nucleotide sequence encodes a polypeptide of 786 amino acids (SEQ ID NO:23) with a predicted molecular mass of 92,037 daltons. Analysis of the deduced amino acid sequence predicts SULU3 to be an intracellular serine/threonine kinase lacking a transmembrane domain. The N-terminally truncated human SULU3 protein contains a 66 amino acid partial catalytic domain followed by a 149 amino acid spacer region, a 210 amino acid region predicted to form a coiled-coil structure, a second spacer region of 114 amino acids, a 247 amino acid C-terminal region predicted to form a second coiled-coil structure and a 100 amino acid C-terminal tail.

Human SULU3 is most closely related murine SULU3 (SEQ ID NO:24), human SULU1 (SEQ ID NO:22), and to the *C. elegans* SULU kinase (GB:U11280), sharing 66.3%, 68.9% and 32.9% amino acid identity, respectively. The high sequence



homology between murine and human SULU3 suggests that these two proteins are orthologs of each other.

The 66 amino acid partial catalytic domain of human SULU3 is most related to murine SULU3 (SEQ ID NO:24), and to the human STE20 subfamily kinases ZC1 (SEQ ID NO:13), STE20 (GB:X99325), KHS1 (GB:U177129) and GEK 2 (SEQ ID NO:107), as well as to the *C. elegans* SULU kinase (GB:U11280), sharing 83.3%, 47.0%, 45.5%, 43.5%, 41.8% and 55.6% amino acid identity, respectively.

The 149 amino acid spacer region of human SULU3 is most related to murine SULU3 (SEQ ID NO:24), human STE20 (GB:X99325), MST1 (GB:U18297), and to the *C.elegans* SULU kinase (GB:U11280) sharing 98.7%, 21.9% and 21.8% amino acid identity, respectively.

Immediately C-terminal to the first spacer region of human SULU3 is a 210 amino acid region predicted to form a coiled-coil structure based on the Lupas algorithm. This region of SULU3 is most related to murine SULU3 (SEQ ID NO:24), and to human SULU1 (SEQ ID NO:22), ZC1 (SEQ ID NO:13) and GEK 2 (SEQ ID NO:107), as well as to the *C. elegans* SULU kinase (GB:U11280), sharing 99.5%, 68.6%, 27.4% and 22.5% amino acid identity, respectively.

The 114 amino acid second spacer region of human SULU3 is most related to murine SULU3 (SEQ ID NO:24), and to human SULU1 (SEQ ID NO:22) GEK 2 (SEQ ID NO:107), and ZC1 (SEQ ID NO:13), as well as to the *C. elegans* SULU kinase (GB:U11280), sharing 99.1%, 73.7%, 24.6%, 24.1% and 41.2% amino acid identity, respectively.

Immediately C-terminal to the second spacer region of human SULU3 is a 247 amino acid region predicted to form a coiled-coil structure based on the Lupas algorithm (supra).

This region of SULU3 is most related to human SULU1 (SEQ ID NO:22) and ZC1 (SEQ ID NO:13) as well as to rat PKN-

(GB:D26180) murine pl60 ROCK1 (GB:U58512), and the *C. elegans* SULK1 kinase (GB:U11280), sharing 73.7%, 26.7%, 24.0% and 21.0% amino acid identity, respectively.

5 The 100 amino acid C-tail of human SULK1 is most related to a human prion protein (GB:L38993), with 45.0% amino acid identity.

#### Mammalian (murine) SULK1

10 The 2249 bp murine, partial cDNA SULK1 nucleotide sequence encodes a polypeptide of 748 amino acids (SEQ ID NO:24) with a predicted molecular mass of 87,520 daltons. Analysis of the deduced amino acid sequence predicts SULK1 to be an intracellular serine/threonine kinase, lacking both a signal sequence and transmembrane domain. The partial  
15 murine SULK1 protein contains a 25 amino acid N-terminus, a 248 amino acid catalytic domain with all the motifs characteristic of a serine/threonine kinase, a 149 amino acid spacer region, a 210 amino acid region predicted to form a coiled-coil structure, and a 116 amino acid spacer  
20 region.

Murine SULK1 is most closely related to human SULK1 (SEQ ID NO:23) and SULK2 (SEQ ID NO:22), as well as to the *C. elegans* SULK1 kinase (GB:U11280), sharing 97.0%, 72.3% and 38.4% amino acid identity, respectively. The high  
25 sequence homology between murine and human SULK1 suggests that these two proteins are orthologs.

The 25 amino acid N-terminal domain of murine SULK1 is most related to human SULK2 (SEQ ID NO:22) and to the *C. elegans* SULK1 kinase (GB:U11280), sharing 70.0% and 44.4%  
30 amino acid identity, respectively.

Murine SULK1 lacks a glycine residue at position 2, and is therefore unlikely to undergo myristoylation. A Smith-Waterman search of the nonredundant protein database does

not reveal any significant homologies that might suggest a potential function for this domain.

The 248 amino acid catalytic domain of murine SULU3 is most related to human SULU1 (SEQ ID NO:22), STE20  
5 (GB:X99325), ZC1 (SEQ ID NO:13), and KHS1 (GB:U77129), as well as to the *C. elegans* SULU kinase (GB:U11280), sharing 86.7%, 46.6%, 43.3%, 59.4% amino acid identity, respectively. Murine SULU3 contains the potential "TPY" regulatory phosphorylation site in its activation loop. This  
10 "TPY" motif is conserved in other STE20-related kinases, including ZC2, ZC3, ZC4, GEK2, KHS2, SULU1, SULU3, PAK4 and PAK5.

The 149 amino acid spacer of murine SULU3 is most related to human SULU3 (SEQ ID NO:23), SULU1 (SEQ ID NO:22),  
15 and STE20 (GB:X99325), as well as to the *C. elegans* SULU (GB:U11280) and the *S. cerevisiae* STE20 (GB:L04655) kinases, sharing 98.7%, 53.4%, 21.9%, 59.4% and 21.9% amino acid identity, respectively.

Immediately C-terminal to the spacer region of murine  
20 SULU3 is a 210 amino acid region predicted to form a coiled-coil structure based on the Lupas algorithm. This region of murine SULU3 is most related to human SULU3 (SEQ ID NO:23), ZC1 (SEQ ID NO:13), and GEK 2 (SEQ ID NO:107), as well as to the *C. elegans* SULU kinase (GB:U11280), sharing 99.5%,  
25 27.4%, 22.5% and 29.2% amino acid identity, respectively.

The 116 amino acid C-terminal spacer region of murine SULU3 is most related to human SULU3 (SEQ ID NO:23), GEK 2 (SEQ ID NO:107), and ZC1 (SEQ ID NO:13), well as to the *C. elegans* SULU kinase (GB:U11280), sharing 98.3%, 24.6%, 24.1%  
30 and 40.5% amino acid identity, respectively.

Mammalian (murine/human) SULU3

The 2249 bp murine SULU3 and the 3824 bp human SULU3 cDNAs contain a 1620 nucleotide overlap (541 amino acids) with 90% and 98% DNA and amino acid sequence identity, respectively. Owing to the high degree of sequence identity in this extended overlap, we propose that these are functional orthologues of a single gene. The combined murine/human 4492 bp SULU3 sequence encodes a polypeptide of 1001 amino acids (SEQ ID NO:31) with a predicted molecular mass of 116,069 daltons. Analysis of the deduced amino acid sequence predicts SULU3 to be an intracellular serine/threonine kinase, lacking both a signal sequence and transmembrane domain. SULU3 contains a 25 amino acid N-terminus, a 248 amino acid catalytic domain with all the motifs characteristic of a serine/threonine kinase, a 149 amino acid spacer region, a 210 amino acid region predicted to form a coiled-coil structure and a second spacer region of 114 amino acids, a 247 amino acid C-terminal region predicted to form a second coiled-coil structure and a 100 amino acid C-terminal tail. The murine SULU3 clone lacks the region from the second C-terminal coiled-coil to the C-terminus, whereas the human clone lacks the N-terminal domain, and all but 66 amino acids of the 248 amino acid kinase domain.

SULU3 is most closely related to SULU1 (SEQ ID NO:22) and the *C. elegans* SULU kinase (GB:U11280) sharing 72.3% and 38.4% amino acid identity, respectively.

The 25 amino acid N-terminal domain of SULU3 is most related to human SULU1 (SEQ ID NO:22) and to the *C. elegans* SULU kinase (GB:U11280), sharing 70.0% and 44.4% amino acid identity, respectively. SULU3 lacks a glycine residue at position 2, and is therefore unlikely to undergo myristylation. A Smith-Waterman search of the nonredundant

protein database does not reveal any significant homologies that might suggest a potential function for this domain.

The 248 amino acid catalytic domain of SULU3 is most related to human SULU1 (SEQ ID NO:22), SOK-1 (GB:X99325), ZC1 (SEQ ID NO:13), KHS1 (GB:U77129) and the *C. elegans* SULU kinase (GB:U11280), sharing 86.7%, 46.6%, 43.3%, 42.0% and 59.4% amino acid identity, respectively. SULU3 contains the potential "TPY" regulatory phosphorylation site in its activation loop. This "TPY" motif is conserved in other STE20-related kinases, including ZC2, ZC3, ZC4, GEK2, KHS2, SULU1, PAK4 and PAK5.

The 149 amino acid spacer of SULU3 is most related to SULU1 (SEQ ID NO:22) and SOK-1 (GB:X99325), and to the *C. elegans* SULU (GB:U11280), and *S. cerevisiae* STE20 (GB:L04655) kinases, sharing 53.4%, 21.9%, 59.4% and 21.9% amino acid identity, respectively.

Immediately C-terminal to the spacer region of SULU3 is a 210 amino acid region predicted to form a coiled-coil structure based on the Lupas algorithm. This region is most related to ZC1 (SEQ ID NO:13), GEK 2 (SEQ ID NO:107), and the *C. elegans* SULU kinase (GB:U11280), sharing 27.4% 22.5% and 29.2% amino acid identity, respectively.

The 114 amino acid spacer region of SULU3 is most related to human SULU1 (SEQ ID NO:22), GEK 2 (SEQ ID NO:107), ZC1 (SEQ ID NO:13), and to the *C. elegans* SULU kinase (GB:U11280), sharing 73.7%, 24.6%, 24.1% and 41.2% amino acid identity, respectively.

Immediately C-terminal to the second spacer region of SULU3 is a 247 amino acid region predicted to form a coiled-coil structure based on the Lupas algorithm. This region of SULU3 is most related to human SULU1 (SEQ ID NO:22) and ZC1 (SEQ ID NO:13), as well as to rat PKN (GB:D26180), murine p160 ROCK1 (GB:U58512) and the *C. elegans* SULU kinase

(GB:U11280), sharing 73.7%, 26.7%, 24.0%, 21.0% and 37.6% amino acid identity, respectively.

The 100 amino acid C-tail of SULU3 is most related to a human prion protein (GB:L38993) with 45.0% amino acid identity.

#### Mammalian GEK2

The 2926 bp human GEK2 nucleotide sequence of the complete cDNA encodes a polypeptide of 968 amino acids (SEQ ID NO:107) with a predicted molecular mass of 112,120 daltons. Analysis of the deduced amino acid sequence predicts GEK2 to be an intracellular serine/threonine kinase, lacking both a signal sequence and transmembrane domain. The complete GEK2 protein contains a 33 amino acid N-terminus, a 261 amino acid catalytic domain with all the motifs characteristic of a serine/threonine kinase, a 43 amino acid spacer region, a 135 amino acid proline-rich region, a 252 amino acid region predicted to form a coiled-coil structure followed by a 244 amino acid region also predicted to form a coiled-coil structure.

GEK2 is most closely related to rat AT1-46 (GB:U33472) (a partial cDNA that extends from the middle of the first potential coiled-coil domain of GEK2 to the C-terminus), murine LOK (GB:D89728), *Xenopus laevis* polo-like kinase 1 (GB:AF100165), and human SLK (GB:AB002804), sharing 91.3%, 88.5%, 65.0%, and 44.7% amino acid identity, respectively. The high sequence homology between human GEK2, murine LOK and rat AT1-46 suggests that human GEK2 is a highly related protein to the rodent forms, or alternatively, its orthologue. Recently, a full-length version of GEK2 was reported (STK10 or human LOK AB015718). The 968 amino acid sequence is 99% identical to GEK2 (SEQ ID NO:107).

The 33 amino acid N-terminal domain of human GEK2 is most related to murine LOK (GB:D89728) and to human SLK (GB:AB002804), sharing 100% and 54.5% amino acid identity, respectively.

5 Human GEK2 lacks a glycine residue at position 2, and is therefore unlikely to undergo myristylation. A Smith-Waterman search of the nonredundant protein database does not reveal any significant homologies that might suggest a potential function for this domain.

10 The 261 amino acid catalytic domain of human GEK2 is most related to murine LOK (GB:D89728), rat AT1-46 (GB:D89728) and human SLK (GB:AB002804) as well as to a *C. elegans* kinase (GB:Z81460), sharing 97.7%, 90.8%, 54.5% and 55.9% amino acid identity, respectively. GEK2 contains the  
15 potential "TPY" regulatory phosphorylation site in its activation loop. This "TPY" motif is conserved in other STE20-related kinases, including ZC2, ZC3, ZC4, GEK2, KHS2, SULU1, SULU3, PAK4 and PAK5.

The 43 amino acid spacer region of human GEK2 is most  
20 related to murine LOK (GB:D89728) and to human SLK, sharing 83.7% and 77.6% amino acid identity, respectively.

The 135 amino acid proline-rich region of human GEK2 is most related to murine LOK (GB:D89728) with 66.2% amino acid identity, respectively. Within the proline-rich region of  
25 human GEK2 is a potential "PxxP" SH3-binding domain conserved with murine LOK.

Immediately C-terminal to the proline-rich region of human GEK2 is a 252 amino acid region predicted to form a coiled-coil structure based on the Lupas algorithm. This  
30 region of human GEK2 is most related to rat AT1-46 (GB:D89728), murine LOK (GB:D89728) and human SLK (GB:AB002804), and ZC2 (SEQ ID NO:14), sharing 90.8%, 86.9%, 42.2%, and 29.7% amino acid identity, respectively.

Immediately C-terminal to the predicted coiled-coil structure of human GEK2 is a second potential coiled-coil structure of 244 amino acids predicted based on the Lupas algorithm. This region of human GEK2 is most related to rat  
5 AT1-46 (GB:D89728) and murine LOK (GB:D89728) as well as to human SLK (GB:AB002804) and ZC1 (SEQ ID NO:13), sharing 91.8%, 92.6%, 70.4% and 26.7% amino acid identity, respectively. The *C. elegans* kinase (GB:Z81460) shares 31.5% amino acid sequence identity over this region.

10

#### Mammalian PAK4

The 3604 bp human PAK4 nucleotide sequence encodes a polypeptide of 681 amino acids (SEQ ID NO:29) with a predicted molecular mass of 74,875 daltons. Analysis of the  
15 deduced amino acid sequence predicts PAK4 to be an intracellular serine/threonine kinase, lacking both a signal sequence and transmembrane domain. The full-length PAK4 protein contains a 51 amino acid N-terminus predicted to contain a rac-binding motif, a 173 amino acid insert  
20 relative to the known mammalian PAK proteins, a 169 amino acid spacer region, a 265 amino acid catalytic domain with all the motifs characteristic of a serine/threonine kinase and a 23 amino acid C-terminal tail.

25

PAK4 is most closely related to human PAK5 (SEQ ID NO:30), PAK1 (GB: U24152), and PAK65 (GB:U25975), as well as to a *C. elegans* kinase (GB: Z74029), sharing 76.8%, 49.5%, 49.8%, and 34.6% amino acid identity, respectively.

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The 51 amino acid N-terminal domain of human PAK4 is most related to human PAK1 (GB:U24152), and PAK65 (GB:U25975), as well as to a *C.elegans* kinase (GB: Z74029), sharing 50.0%, 50.0% and 49.0% amino acid identity, respectively.



The 11 amino acid region at positions 13-23 of human PAK4 fits the consensus for a Cdc42/Rac-binding motif (SXPX4-6HXXH) (Burbelo, P.D., Dreschel, D. and Hall, A. J. Bio. Chem. 270, 29071-29074 (1995)).

5       The 173 amino acid insert of human PAK4, relative to the known mammalian PAK proteins, is most related to a *C. elegans* kinase (GB: Z74029) with 39.0% amino acid identity.

10       A Smith-Waterman search of the nonredundant protein database does not reveal any significant homologies that might suggest a potential function for this region.

      The 169 amino acid spacer of human PAK4 does not reveal any significant homologies that might suggest a potential function for this region.

15       The equivalent spacer region in PAK1 binds to the guanine nucleotide exchange factor PIX (Manser, E. et al (1998) Molecular Cell, 1, 183-192). Since PAK4 differs substantially from PAK1 over this region, the spacer domain of PAK4 may differ in its guanine nucleotide exchange factor binding specificity, relative to PAK1.

20       The 265 amino acid catalytic domain of human PAK4 is most related to human PAK5 (SEQ ID NO:30), PAK1 (GB:U24152), GCK (GB:U07349), SOK-1 (GB:X99325), and SLK (GB:AB002804), as well as to the *C. elegans* (GB: Z74029), and *S. cerevisiae* STE20-related kinases (GB:L04655), sharing 95.9%, 51.7%,  
25       41.3%, 39.8%, 37.4%, 60.2% and 47.9% amino acid identity, respectively. PAK4 contains the potential "TPY" regulatory phosphorylation site in its activation loop. This "TPY" motif is conserved in other STE20-related kinases, including ZC1, ZC2, ZC3, ZC4, GEK2, KHS2, SULU1, SULU3 and PAK5.

30       The 23 amino acid C-tail of human PAK4 contains a sequence that is homologous to a G-protein beta subunit binding site (Leeuw, T. et al. Nature, 391, 191-195 (1998)).

PAK4 has, therefore, the potential to be activated by both Cdc42- as well as G-protein-dependant pathways.

#### Mammalian PAK5

5           The 2,806 bp human PAK5 nucleotide sequence of the complete cDNA encodes a polypeptide of 591 amino acids (SEQ ID NO:103) with a predicted molecular mass of 64,071 Daltons. Analysis of the deduced amino acid sequence predicts PAK5 to be an intracellular STE20-subfamily kinase, 10           lacking both a signal sequence and transmembrane domain. The full-length PAK5 protein contains a 52 amino acid N-terminus predicted to contain a p21 (small G-protein) binding domain (PDB or CRIB), a 121 amino acid insert relative to the known mammalian PAK proteins, a 134 amino 15           spacer region, a 265 amino acid catalytic domain with all the motifs characteristic of a serine/threonine kinase and a 19 amino acid C-terminal tail.

PAK5 is most closely related to Human PAK4 (SEQ ID NO:29), *Drosophila melanogaster* PAK (also known as "mushroom 20           bodies tiny") (AJ011578), C45B11.1b from *C. elegans* (Z74029), and human PAK3 (Q13177) sharing 48% (327/674 aa), 50% (330/651 aa), 43% (234/435 aa excluding gap), and 47% (190/405 aa excluding gap) amino acid identity, respectively. Recently, a full length version of PAK5 was 25           reported (PAK4 AF005046) whose 591 amino acid sequence is identical to PAK5 (SEQ ID NO:103). (Abo, et al. (1998) EMBO J. 17:6527-6540).

30           The 52 amino acid N-terminal domain of human PAK5 is most related to human PAK4 (SEQ ID NO:29), *Drosophila melanogaster* PAK (AJ011578), C45B11.1b from *C. elegans* (Z74029), and human PAK3 (Q13177), sharing 65%, 57%, 54%, and 53% amino acid identity, respectively.

The 11 amino acid region at positions 12-22 of human PAK5 (FIG. 18) fits the consensus for a small G-protein binding domain (PDB or CRIB) (SXPX4-6HXXH) (Burbelo, P.D., Dreschel, D. and Hall, A. J. Bio. Chem. 270, 29071-29074 (1995), hereby incorporated by reference herein in its entirety including any figures, tables, or drawings.).

The 121 amino acid insert of human PAK5 shares 43% amino acid identity with a similar domain from PAK4 (SEQ ID NO:29), but that is absent from other known PAKs.

The equivalent spacer region in PAK1 binds to the guanine nucleotide exchange factor PIX (Manser, E. et al (1998) Molecular Cell, 1, 183-192 hereby incorporated by reference herein in its entirety including any drawings, figures, or tables.). Since PAK5 differs substantially from PAK1 over this region, the spacer domain of PAK5 may differ in its guanine nucleotide exchange factor binding specificity, relative to PAK1.

The 134 amino acid collagen-like region of human PAK5 shares 34% amino acid identity to pro- $\alpha$  I type collagen from several species and is not present in other known PAKs.

The 265 amino acid catalytic domain of human PAK5 is most related to human PAK4 (SEQ ID NO:29), *Drosophila melanogaster* PAK (AJ011578), C45B11.1b from *C. elegans* (Z74029), and human PAK3 (Q13177), sharing 78%, 80%, 61%, and 55% amino acid identity, respectively. PAK5 also contains the potential "TPY" regulatory phosphorylation site in its activation loop. This "TPY" motif is conserved in other STE20-related kinases, including ZC1, ZC2, ZC3, ZC4, GEK2, KHS2, SULU1, SULU3 and PAK4.

The 19 amino acid C-tail shares 80% amino acid identity to a PAK-like homologue identified from genomic DNA (AL031652). Furthermore, this C-terminal region of human PAK5 contains a sequence that is homologous to a G-protein

beta subunit binding site (Leeuw, T. et al. Nature, 391, 191-195 (1998) hereby incorporated by reference herein in its entirety including any figures, tables, or drawings). PAK5 has, therefore, the potential to be activated by both, Cdc42 as well as G-protein-dependant pathways.

V. Antibodies, Hybridomas, Methods of Use and Kits for Detection of STE20-Related Kinases

The present invention relates to an antibody having binding affinity to a kinase of the invention. The polypeptide may have the amino acid sequence set forth in SEQ ID NO:5, SEQ ID NO:6, SEQ ID NO:7, SEQ ID NO:13, SEQ ID NO:14, SEQ ID NO:15, SEQ ID NO:18, SEQ ID NO:22, SEQ ID NO:23, SEQ ID NO:24, SEQ ID NO:29, SEQ ID NO:97, SEQ ID NO:99, SEQ ID NO:101, SEQ ID NO:103, SEQ ID NO:105, or SEQ ID NO:107, or a functional derivative thereof, or at least 9 contiguous amino acids thereof (preferably, at least 20, 30, 35, or 40 or more contiguous amino acids thereof).

The present invention also relates to an antibody having specific binding affinity to a kinase of the invention. Such an antibody may be isolated by comparing its binding affinity to a kinase of the invention with its binding affinity to other polypeptides. Those which bind selectively to a kinase of the invention would be chosen for use in methods requiring a distinction between a kinase of the invention and other polypeptides. Such methods could include, but should not be limited to, the analysis of altered kinase expression in tissue containing other polypeptides.

The STE20-Related kinases of the present invention can be used in a variety of procedures and methods, such as for the generation of antibodies, for use in identifying

pharmaceutical compositions, and for studying DNA/protein interaction.

5 The kinases of the present invention can be used to produce antibodies or hybridomas. One skilled in the art will recognize that if an antibody is desired, such a peptide could be generated as described herein and used as an immunogen. The antibodies of the present invention include monoclonal and polyclonal antibodies, as well fragments of these antibodies, and humanized forms.

10 Humanized forms of the antibodies of the present invention may be generated using one of the procedures known in the art such as chimerization or CDR grafting.

The present invention also relates to a hybridoma which produces the above-described monoclonal antibody, or binding fragment thereof. A hybridoma is an immortalized cell line which is capable of secreting a specific monoclonal antibody.

15

In general, techniques for preparing monoclonal antibodies and hybridomas are well known in the art (Campbell, "Monoclonal Antibody Technology: Laboratory Techniques in Biochemistry and Molecular Biology," Elsevier Science Publishers, Amsterdam, The Netherlands, 1984; St. Groth et al., J. Immunol. Methods 35:1-21, 1980). Any animal (mouse, rabbit, and the like) which is known to produce antibodies can be immunized with the selected polypeptide. Methods for immunization are well known in the art. Such methods include subcutaneous or intraperitoneal injection of the polypeptide. One skilled in the art will recognize that the amount of polypeptide used for immunization will vary based on the animal which is immunized, the antigenicity of the polypeptide and the site of injection.

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The polypeptide may be modified or administered in an adjuvant in order to increase the peptide antigenicity. Methods of increasing the antigenicity of a polypeptide are well known in the art. Such procedures include coupling the antigen with a heterologous protein (such as globulin or  $\beta$ -galactosidase) or through the inclusion of an adjuvant during immunization.

For monoclonal antibodies, spleen cells from the immunized animals are removed, fused with myeloma cells, such as SP2/0-Ag14 myeloma cells, and allowed to become monoclonal antibody producing hybridoma cells. Any one of a number of methods well known in the art can be used to identify the hybridoma cell which produces an antibody with the desired characteristics. These include screening the hybridomas with an ELISA assay, western blot analysis, or radioimmunoassay (Lutz et al., Exp. Cell Res. 175:109-124, 1988). Hybridomas secreting the desired antibodies are cloned and the class and subclass are determined using procedures known in the art (Campbell, "Monoclonal Antibody Technology: Laboratory Techniques in Biochemistry and Molecular Biology", supra, 1984).

For polyclonal antibodies, antibody-containing antisera is isolated from the immunized animal and is screened for the presence of antibodies with the desired specificity using one of the above-described procedures. The above-described antibodies may be detectably labeled. Antibodies can be detectably labeled through the use of radioisotopes, affinity labels (such as biotin, avidin, and the like), enzymatic labels (such as horse radish peroxidase, alkaline phosphatase, and the like) fluorescent labels (such as FITC or rhodamine, and the like), paramagnetic atoms, and the like. Procedures for accomplishing such labeling are well-known in the art, for example, see Stemberger et al., J.

Histochem. Cytochem. 18:315, 1970; Bayer et al., Meth. Enzym. 62:308-, 1979; Engval et al., Immunol. 109:129-, 1972; Goding, J. Immunol.\_Meth. 13:215-, 1976. The labeled antibodies of the present invention can be used for in vitro, in vivo, and in situ assays to identify cells or tissues which express a specific peptide.

The above-described antibodies may also be immobilized on a solid support. Examples of such solid supports include plastics such as polycarbonate, complex carbohydrates such as agarose and sepharose, acrylic resins and such as polyacrylamide and latex beads. Techniques for coupling antibodies to such solid supports are well known in the art (Weir et al., "Handbook of Experimental Immunology" 4th Ed., Blackwell Scientific Publications, Oxford, England, Chapter 10, 1986; Jacoby et al., Meth. Enzym. 34, Academic Press, N.Y., 1974). The immobilized antibodies of the present invention can be used for in vitro, in vivo, and in situ assays as well as in immunochromatography.

Furthermore, one skilled in the art can readily adapt currently available procedures, as well as the techniques, methods and kits disclosed herein with regard to antibodies, to generate peptides capable of binding to a specific peptide sequence in order to generate rationally designed antipeptide peptides (Hurby et al., "Application of Synthetic Peptides: Antisense Peptides", In Synthetic Peptides, A User's Guide, W.H. Freeman, NY, pp. 289-307, 1992; Kaspczak et al., Biochemistry 28:9230-9238, 1989).

Anti-peptide peptides can be generated by replacing the basic amino acid residues found in the peptide sequences of the kinases of the invention with acidic residues, while maintaining hydrophobic and uncharged polar groups. For example, lysine, arginine, and/or histidine residues are

replaced with aspartic acid or glutamic acid and glutamic acid residues are replaced by lysine, arginine or histidine.

The present invention also encompasses a method of detecting a STE20-related kinase polypeptide in a sample, comprising: (a) contacting the sample with an above-described antibody, under conditions such that immunocomplexes form, and (b) detecting the presence of said antibody bound to the polypeptide. In detail, the methods comprise incubating a test sample with one or more of the antibodies of the present invention and assaying whether the antibody binds to the test sample. Altered levels of a kinase of the invention in a sample as compared to normal levels may indicate disease.

Conditions for incubating an antibody with a test sample vary. Incubation conditions depend on the format employed in the assay, the detection methods employed, and the type and nature of the antibody used in the assay. One skilled in the art will recognize that any one of the commonly available immunological assay formats (such as radioimmunoassays, enzyme-linked immunosorbent assays, diffusion based Ouchterlony, or rocket immunofluorescent assays) can readily be adapted to employ the antibodies of the present invention. Examples of such assays can be found in Chard ("An Introduction to Radioimmunoassay and Related Techniques" Elsevier Science Publishers, Amsterdam, The Netherlands, 1986), Bullock et al. ("Techniques in Immunocytochemistry," Academic Press, Orlando, FL Vol. 1, 1982; Vol. 2, 1983; Vol. 3, 1985), Tijssen ("Practice and Theory of Enzyme Immunoassays: Laboratory Techniques in Biochemistry and Molecular Biology," Elsevier Science Publishers, Amsterdam, The Netherlands, 1985).

The immunological assay test samples of the present invention include cells, protein or membrane extracts of



cells, or biological fluids such as blood, serum, plasma, or urine. The test samples used in the above-described method will vary based on the assay format, nature of the detection method and the tissues, cells or extracts used as the sample to be assayed. Methods for preparing protein extracts or membrane extracts of cells are well known in the art and can be readily be adapted in order to obtain a sample which is testable with the system utilized.

A kit contains all the necessary reagents to carry out the previously described methods of detection. The kit may comprise: (i) a first container means containing an above-described antibody, and (ii) second container means containing a conjugate comprising a binding partner of the antibody and a label. In another preferred embodiment, the kit further comprises one or more other containers comprising one or more of the following: wash reagents and reagents capable of detecting the presence of bound antibodies.

Examples of detection reagents include, but are not limited to, labeled secondary antibodies, or in the alternative, if the primary antibody is labeled, the chromophoric, enzymatic, or antibody binding reagents which are capable of reacting with the labeled antibody. The compartmentalized kit may be as described above for nucleic acid probe kits. One skilled in the art will readily recognize that the antibodies described in the present invention can readily be incorporated into one of the established kit formats which are well known in the art.

VI. Isolation of Compounds Which Interact With STE20-  
Related Kinases

The present invention also relates to a method of detecting a compound capable of binding to a STE20-related kinase of the invention comprising incubating the compound with a kinase of the invention and detecting the presence of the compound bound to the kinase. The compound may be present within a complex mixture, for example, serum, body fluid, or cell extracts.

The present invention also relates to a method of detecting an agonist or antagonist of kinase activity or kinase binding partner activity comprising incubating cells that produce a kinase of the invention in the presence of a compound and detecting changes in the level of kinase activity or kinase binding partner activity. The compounds thus identified would produce a change in activity indicative of the presence of the compound. The compound may be present within a complex mixture, for example, serum, body fluid, or cell extracts. Once the compound is identified it can be isolated using techniques well known in the art.

The present invention also encompasses a method of agonizing (stimulating) or antagonizing kinase associated activity in a mammal comprising administering to said mammal an agonist or antagonist to a kinase of the invention in an amount sufficient to effect said agonism or antagonism. A method of treating diseases in a mammal with an agonist or antagonist of STE20-related kinase activity comprising administering the agonist or antagonist to a mammal in an amount sufficient to agonize or antagonize STE20-related kinase associated functions is also encompassed in the present application.

In an effort to discover novel treatments for diseases, biomedical researchers and chemists have designed, synthesized, and tested molecules that inhibit the function of protein kinases. Some small organic molecules form a class of compounds that modulate the function of protein kinases. Examples of molecules that have been reported to inhibit the function of protein kinases include, but are not limited to, bis monocyclic, bicyclic or heterocyclic aryl compounds (PCT WO 92/20642, published November 26, 1992 by Maguire et al.), vinylene-azaindole derivatives (PCT WO 94/14808, published July 7, 1994 by Ballinari et al.), 1-cyclopropyl-4-pyridyl-quinolones (U.S. Patent No. 5,330,992), styryl compounds (U.S. Patent No. 5,217,999), styryl-substituted pyridyl compounds (U.S. Patent No. 5,302,606), certain quinazoline derivatives (EP Application No. 0 566 266 A1), seleoindoles and selenides (PCT WO 94/03427, published February 17, 1994 by Denny et al.), tricyclic polyhydroxylic compounds (PCT WO 92/21660, published December 10, 1992 by Dow), and benzylphosphonic acid compounds (PCT WO 91/15495, published October 17, 1991 by Dow et al).

Compounds that can traverse cell membranes and are resistant to acid hydrolysis are potentially advantageous as therapeutics as they can become highly bioavailable after being administered orally to patients. However, many of these protein kinase inhibitors only weakly inhibit the function of protein kinases. In addition, many inhibit a variety of protein kinases and will cause multiple side-effects as therapeutics for diseases.

Some indolinone compounds, however, form classes of acid resistant and membrane permeable organic molecules. WO 96/22976 (published August 1, 1996 by Ballinari et al.) describes hydrosoluble indolinone compounds that harbor

5 tetralin, naphthalene, quinoline, and indole substituents fused to the oxindole ring. These bicyclic substituents are in turn substituted with polar moieties including hydroxylated alkyl, phosphate, and ether moieties. U.S. Patent Application Serial Nos. 08/702,232, filed August 23, 1996, entitled "Indolinone Combinatorial Libraries and Related Products and Methods for the Treatment of Disease" by Tang et al. (Lyon & Lyon Docket No. 221/187) and 08/485,323, filed June 7, 1995, entitled "Benzylidene-Z-Indoline Compounds for the Treatment of Disease" and International Patent Publication WO 96/22976, published August 1, 1996 by al. (Lyon & Lyon Docket No. 223/298) and International Patent Publication WO 96/22976, published August 1, 1996 by Ballinari et al., all of which are incorporated herein by reference in their entirety, including any drawings, describe indolinone chemical libraries as well as compounds harboring other bicyclic moieties as well as monocyclic moieties fused to the oxindole ring. 15 Applications 08/702,232, filed August 23, 1996, entitled "Indolinone Combinatorial Libraries and Related Products and Methods for the Treatment of Disease" by Tang et al. (Lyon & Lyon Docket No. 221/187), 08/485,323, filed June 7, 1995, entitled "Benzylidene-Z-Indoline Compounds for the Treatment of Disease" by Tang et al. (Lyon & Lyon Docket No. 223/298), and WO 96/22976, published August 1, 1996 by Ballinari et al. teach methods of indolinone synthesis, methods of testing the biological activity of indolinone compounds in cells, and inhibition patterns of indolinone derivatives. 25 Other examples of substances capable of modulating kinase activity include, but are not limited to, tyrphostins, quinazolines, quinoxolines, and quinolines. The quinazolines, tyrphostins, quinolines, and quinoxolines referred to above include well known compounds such as those described in the literature. For example, representative

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publications describing quinazolines include Barker et al., EPO Publication No. 0 520 722 A1; Jones et al., U.S. Patent No. 4,447,608; Kabbe et al., U.S. Patent No. 4,757,072; Kaul and Vougioukas, U.S. Patent No. 5, 316,553; Kreighbaum and Comer, U.S. Patent No. 4,343,940; Pegg and Wardleworth, EPO Publication No. 0 562 734 A1; Barker et al., Proc. of Am. Assoc. for Cancer Research 32:327 (1991); Bertino, J.R., Cancer Research 3:293-304 (1979); Bertino, J.R., Cancer Research 9(2 part 1):293-304 (1979); Curtin et al., Br. J. Cancer 53:361-368 (1986); Fernandes et al., Cancer Research 43:1117-1123 (1983); Ferris et al. J. Org. Chem. 44(2):173-178; Fry et al., Science 265:1093-1095 (1994); Jackman et al., Cancer Research 51:5579-5586 (1991); Jones et al. J. Med. Chem. 29(6):1114-1118; Lee and Skibo, Biochemistry 26(23):7355-7362 (1987); Lemus et al., J. Org. Chem. 54:3511-3518 (1989); Ley and Seng, Synthesis 1975:415-522 (1975); Maxwell et al., Magnetic Resonance in Medicine 17:189-196 (1991); Mini et al., Cancer Research 45:325-330 (1985); Phillips and Castle, J. Heterocyclic Chem. 17(19):1489-1596 (1980); Reece et al., Cancer Research 47(11):2996-2999 (1977); Sculier et al., Cancer Immunol. and Immunother. 23:A65 (1986); Sikora et al., Cancer Letters 23:289-295 (1984); Sikora et al., Analytical Biochem. 172:344-355 (1988); all of which are incorporated herein by reference in their entirety, including any drawings.

Quinoxaline is described in Kaul and Vougioukas, U.S. Patent No. 5,316,553, incorporated herein by reference in its entirety, including any drawings.

Quinolines are described in Dolle et al., J. Med. Chem. 37:2627-2629 (1994); McGuire, J. Med. Chem. 37:2129-2131 (1994); Burke et al., J. Med. Chem. 36:425-432 (1993); and Burke et al. BioOrganic Med. Chem. Letters 2:1771-1774

(1992), all of which are incorporated by reference in their entirety, including any drawings.

Tyrphostins are described in Allen et al., Clin. Exp. Immunol. 91:141-156 (1993); Anafi et al., Blood 82:12:3524-3529 (1993); Baker et al., J. Cell Sci. 102:543-555 (1992); Bilder et al., Amer. Physiol. Soc. pp. 6363-6143:C721-C730 (1991); Brunton et al., Proceedings of Amer. Assoc. Cancer Rsch. 33:558 (1992); Bryckaert et al., Experimental Cell Research 199:255-261 (1992); Dong et al., J. Leukocyte Biology 53:53-60 (1993); Dong et al., J. Immunol. 151(5):2717-2724 (1993); Gazit et al., J. Med. Chem. 32:2344-2352 (1989); Gazit et al., " J. Med. Chem. 36:3556-3564 (1993); Kaur et al., Anti-Cancer Drugs 5:213-222 (1994); Kaur et al., King et al., Biochem. J. 275:413-418 (1991); Kuo et al., Cancer Letters 74:197-202 (1993); Levitzki, A., The FASEB J. 6:3275-3282 (1992); Lyall et al., J. Biol. Chem. 264:14503-14509 (1989); Peterson et al., The Prostate 22:335-345 (1993); Pillemer et al., Int. J. Cancer 50:80-85 (1992); Posner et al., Molecular Pharmacology 45:673-683 (1993); Rendu et al., Biol. Pharmacology 44(5):881-888 (1992); Sauro and Thomas, Life Sciences 53:371-376 (1993); Sauro and Thomas, J. Pharm. and Experimental Therapeutics 267(3):119-1125 (1993); Wolbring et al., J. Biol. Chem. 269(36):22470-22472 (1994); and Yoneda et al., Cancer Research 51:4430-4435 (1991); all of which are incorporated herein by reference in their entirety, including any drawings.

Other compounds that could be used as modulators include oxindolinones such as those described in U.S. patent application Serial No. 08/702,232 filed August 23, 1996, incorporated herein by reference in its entirety, including any drawings.

VII. Biological Significance, Applications and ClinicalRelevance of Novel STE20-Related KinasesHuman STLK2, STLK3, STLK4, STLK5, STLK6, and STLK7

STLK2, STLK4, STLK5, STLK6 and STLK7 belong to an  
5 expanding family of intracellular STKs that have varying  
degrees of sequence homology to SOK-1, a kinase implicated  
in oxidative stress agents (Pombo, CM et al, EMBO J. (17)  
4537-4546, 1996). Our data shows that STLK2 is expressed  
highly in hematopoietic cells. Therefore, STLK2 may  
10 participate in the oxidative response pathway during  
inflammation. In addition, STLK2 could also be a possible  
component in the signaling pathways leading to T cell  
activation. High levels of STLK2 in several tumor cell  
lines could also imply that STLK2 might be involved in  
15 tumorigenesis.

STLK2 is most closely related to two human STE20-  
subfamily kinases: MST3 and SOK-1. MST3 is a 52,000  
daltons cytoplasmic kinase that is ubiquitously expressed  
with its highest levels of expression found in heart,  
20 skeletal muscle and pancreas. The serine/threonine kinase  
activity of MST3 is activated by phosphorylation. Unlike  
SOK-1, MST3 prefers  $Mn^{++}$  over  $Mg^{++}$  and can use both GTP and  
ATP as phosphate donors. MST3 may undergo dimerization. No  
agonists have yet been identified that activate MST3. The  
25 downstream signaling mechanism of this kinase is unknown  
(Schinkmann, K and Blenis, J. (1997) J. Biol. Chem. 272,  
28695-28703).

SOK-1 is a 50,000 daltons cytoplasmic kinase expressed  
predominantly in testis, large intestine, brain and stomach  
30 and to a lesser extent in heart and lung. SOK-1 is also  
expressed in the germinal center B-cell line (RAMOS) and in  
a mature B cell line (HS Sultan). The serine/threonine  
kinase activity of SOK-1 is activated by phosphorylation.

The C-terminus of SOK-1 has been shown to be inhibitory to the catalytic activity of this kinase. The only agonists known to activate SOK-1 are oxidant agents, like H<sub>2</sub>O<sub>2</sub> and menadione, a quinone that is a potent intracellular generator of reactive oxygen species (Pombo, C.M. et al. EMBO J. 15, 4537-4546). SOK-1 is also activated by chemical anoxia through the generation of reactive oxygen species and release of calcium into the cytoplasm from intracellular stores. SOK-1, therefore, may play an important role in ischemia, the cause of myocardial infarction, stroke and acute renal failure (Pombo, C.M. et al. J. Biol. Chem. 272, 29372-29379 (1997)). The activity of SOK-1 in the response to oxidant stress is inversely correlated with the activity of the stress-activated protein kinases (SAPKs): elevated SOK-1 activity correlates with absent SAPK activity and vice-versa. SOK-1 does not activate any of the four MAP kinase pathways, SAPKs, p38, ERK-1 or MEK-5/ERK-5 (Pombo, C.M. et al. EMBO J. 15, 4537-4546). The downstream signaling mechanism of this kinase remains unknown.

STLK2 is expressed in a wide variety of immune cell types and tissues including thymus, dendrocytes, mast cells, monocytes, B cells (primary, Jurkat, RPMI, SR), T cells (CD8/CD4+, TH1, TH2, CEM, MOLT4) and megakaryocytes (K562), whereas STLK3 is restricted to thymus and STLK4 is predominately expressed in thymus, T cells (CD4/CD8+, TH1, CEM) and B cells (Jurkat, RPMI). Consequently, these STKs might participate in the oxidative response pathway during inflammation, reperfusion injury (stroke, surgery, shock), TNF $\alpha$ -mediated signaling, insulin desensitization, atherogenesis, vascular injury, T or B cell costimulation, or alternatively, participate in other MAPK-related signal transduction processes.



STLK5 is more distantly related to this STE20-subfamily including SOK-1 and STLK2, STLK3 and STLK4. STLK5, may therefore mediate a signaling pathway that is distinct from the oxidative stress response pathway.

5 The high degree of sequence homology in the C-termini of SOK-1, STLK2, STLK3, STLK4, STLK5, and STLK6 raises the possibility that these novel STKs, like SOK-1, may be subject to autoinhibition through a conserved C-terminal motif.

10

Human ZC1, ZC2, ZC3 and ZC4

ZC1 is a good candidate for any disease in which tyrosine kinase, cytokine, or heterotrimeric G-protein coupled receptors have been implicated. The mouse homologue  
15 binds to NCK, and is recruited to activated PDGF (Su et al., EMBO 16: 1279-1290, 1997). The Drosophila homolog has been shown to bind to TRAF2, implicating it in TNF- $\alpha$  signaling (Liu et al., (1999) Curr. Biol. 9:101-104, 1999)).

While ZC1 does not contain the exact NCK- and TRAF2-binding  
20 domains, it is likely to bind to related proteins.

Of the ZC subfamily of STE20-related protein kinases, ZC1 has very broad over-expression in many tumor types, suggesting that it may be involved in cellular growth, transformation, or tumor progression. A truncated form of  
25 ZC1 containing only the C-terminal putative MEKK1-binding domain was found to reduce the number of foci generated by H-Ras-V12 in Rat Intestinal Epithelial cells (RIE-1). These data indicate that ZC1 may play a role in the ability for these cells to overcome contact inhibition and anchorage-  
30 dependent growth.

The ZC1 homolog, Misshapen (*msn*) in *Drosophila melanogaster* was cloned as a result of complementing a mutation in a developmental pathway required for dorsal

closure, a process involving changes in cell shape and position in the embryo (Treisman et al. Gene 186 119-125, 1997). A *D. melanogaster* homolog of the JNK1/JNK2 kinases from mammals was shown to function downstream of *msn* in the dorsal-closure signaling pathway (Su et al. Genes Dev. 12:2371-2380, 1998).

While ZC1 could be involved in multiple aspects of tumorigenesis, by analogy with *Drosophila*, the role of *misshapen* in dorsal closure suggests a critical role in the regulation of the cytoskeleton for the processes of cell attachment, cell movement and perhaps migration.

The association of the ZC1 family members *msn* and NIK with TRAF2 may indicate a role for this kinase in cell survival and/or in apoptosis. The ZC1 family contains a highly conserved domain that in the mouse homolog, NIK, has been shown to bind to MEKK1 (Mitogen-activated/ Extracellular-regulated Kinase Kinase 1) (Su et al., (1997) EMBO 16(6): 1279-90). MEKK1 is involved in cell survival and/or apoptosis in several systems (Schlesinger et al., Front. Biosci. 3:D1181-6, 1998). Depending on the context, MEKK1 appears to be upstream of either the ERK1/MAPK or the JNK/SAPK pathway [Schlesinger et al., (1998 Front. Biosci. 3:D1181-6). Three homologues of ZC1: murine NIK (NCK-interacting kinase) (Su et al. EMBO 16:1279-90, 1997), *Drosophila msn* (Liu et al. Curr. Biol. 9:101-104, 1999) and human HGK (HPK/GCK-like kinase) (Yao et al., J. Biol. Chem. 274:2118-25, 1999) have all been shown to activate the JNK pathway when over-expressed in 293T cells.

ZC1 shares a high degree of homology with these other family members in both the kinase domain and the "MEKK"-binding domains, yet it differs in the intervening region, which contains several putative binding domains for upstream signaling adapter molecules (e.g. NCK, TRAF2). Unlike the

other family members, ZC1 does not appear to activate the JNK pathway in 293T cells as seen by its ability to induce expression of either a JUN or ATF2-driven luciferase gene. Upon co-transfection into these cells with HA-tagged JNK, 5 modest activation of JNK was detected. ZC1 also modestly activated co-transfected ERK1. Both the ERK and the JNK activation were very slight compared with the positive controls in the assay (activated forms of MEK1 and MEKK1, respectively). In both cases, activation required the full- 10 length kinase. While the kinase domain alone is up to 5x more active in autophosphorylation and in phosphorylation of MBP, it does not lead to activation of these potential downstream kinases. Based on the strong sequence homology of ZC1 with the other family members, it is very likely that 15 ZC1 will be important for either JNK or ERK activation once the proper context is found.

ZC1 profoundly inhibits ERK1 kinase expression in co-transfection assays. This effect is dependent on ZC1 kinase activity, occurring with the wild-type and the kinase domain 20 alone, but not with the kinase-dead mutant even though all three forms of ZC1 are expressed at similar levels. This may suggest a role for this kinase in transcriptional or post-transcriptional regulation.

ZC1 may be an important component in the signaling 25 pathways mediated by the co-stimulatory receptor CD28 in T cells and/or by the pro-inflammatory cytokine TNF $\alpha$ , since co-transfection of the wild-type ZC1 activated the RE/AP-luciferase and NF $\kappa$ B-luciferase reporter genes. While our data showed that ZC1 strongly activates NF $\kappa$ B in T-cells, no 30 activation of NF $\kappa$ B driven luciferase was detectable in NIH 3T3 cells. A recent paper (J. Biol. Chem. 274:2118-25; 1999.) has shown that a human ZC1 splicing isoform, HGK, is involved in the TNF $\alpha$ -signaling pathways.

Given the importance of T cell activation in autoimmunity and transplantation, as well as the key role that TNF $\alpha$  plays in inflammatory diseases, it is possible that ZC1 could be a therapeutic target for immunological diseases which include but are not limited to: rheumatoid arthritis, chronic inflammatory bowel diseases (ie Crohn's disease), chronic inflammatory pelvic disease, multiple sclerosis, asthma, osteoarthritis, psoriasis, atherosclerosis, rhinitis, and autoimmunity as well as organ transplantation and cardiovascular diseases.

ZC1 appears to be the human orthologue of murine NIK and possibly an orthologue of a *C. elegans* STE20-subfamily kinase encoded by the ZC504.4 cosmid.

Murine NIK is a 140,000 daltons kinase that is most highly expressed in brain and heart. NIK interacts with the SH3 domains of the adaptor molecule Nck through its proline-rich regions found in the C-terminal extra-catalytic region.

The specific regions that mediate this interaction are two PxxP motifs that are nearly uniformly conserved between NIK, ZC1,2,3 and the *C. elegans* STE20 ZC504.4 kinase. In addition, NIK binds MEKK1 through its 719 amino acid C-terminal (Su, Y-C. et al. (1997) EMBO J. 16, 1279-1290). MEKK1 is a membrane-associated kinase responsible for activating MKK4 (also known as SEK1), which in turn activates SAPK (Yan, M et al. (1994) Nature, 372, 798-800).

NIK may function as a kinase that links growth factor activated pathways and the stress-response pathway mediated by SAPKs. According to this hypothesis, activation of growth factor receptors leads to receptor tyrosine phosphorylation, Nck binding to the phosphorylated tyrosines via its SH2 domain, NIK redistribution to a membrane compartment via binding to the SH3 domain of Nck, and juxtaposition to the membrane-associated MEKK1. The NIK-

MEKK1 interaction would, in this fashion, turn on the SAPK pathway in response to growth factor stimulation (Su, Y-C. et al. (1997) EMBO J. 16, 1279-1290).

5        Given the high homology between ZC1, ZC2, ZC3, and ZC4  
STKs and NIK, it is conceivable that these kinases may each  
function to connect growth factor- and stress-activated  
signaling pathways. The heterogeneity that the ZC kinases  
exhibit within their putative SH3-binding domain could  
10        provide signaling specificity in terms of the nature of the  
adaptor molecule that they bind. The high level of sequence  
conservation in the C-termini of the ZC1, ZC2 and ZC3  
strongly suggests that these human kinases, like murine NIK,  
also may bind to MEKK1 and activate SAPKs. The ZC kinases  
also display strong homology at their C-termini to protein  
15        domains that bind small GTPase proteins such as Rab, Rho and  
Rac. For example, the C-termini of ZC1 is 36.2% identical  
to citron, a murine Rho-binding protein, and 23.1% identical  
to the rab-binding region of GC kinase. This suggests that,  
in addition to adaptor molecules, small GTPase proteins may  
20        also mediate membrane association and activation of the ZC  
kinases. The presence of a potential coiled-coil region  
located immediately C-terminal to the catalytic region  
strongly suggests that the ZC kinases may also be subject to  
regulation via homo or heterodimerization events.

25        The *C. elegans* STE20 ZC504.4 kinase is the product of  
the mig-15 gene. The product of this gene has been  
implicated in several developmental processes such as  
epidermal development, Q neuroblast migrations and muscle  
arm targeting in the developing worm (Zhu, X. and Hedgecock  
30        E. (1997) Worm Breeder's Gazette 14, 76). The high level of  
sequence conservation between the ZC kinases and the ZC504.4  
*C. elegans* kinase will make *C. elegans* a valuable model

organism to study, through epistatic analysis, the signaling properties of the human ZC kinases.

Human KHS2

5           KHS1 (kinase homologous to SPS1/STE20) is a 100,000 dalton cytoplasmic STK that is expressed ubiquitously. KHS1 has been implicated in the mechanism of SAPK activation in response to inflammatory cytokines such as TNF $\alpha$  as well as to ultraviolet light, which also uses the TNF signaling pathway. TNF $\alpha$  binding to its receptors (TNFR1 and TNFR2) results in the sequential association with the receptor C-tail of multiple signaling molecules including TNFR1-associated death domain protein (TRADD), Fas-associated death domain protein (FADD or MORT1), TNFR-associated factor 2 (TRAF2), and the STK RIP (receptor interacting protein). 10           The TRADD-TRAF2 interaction is mediated by a conserved region present at the C-terminus of TRAF2, the TRAF domain. Activation of the NF $\kappa$ B and SAPK pathways is mediated by the ring finger motif present at the N-terminus of TRAF2 (Curr. Opinion in Cell. Biol. (1997) 9:247-251). KHS1 is activated by TNF $\alpha$  stimulation in a TRAF2-dependant manner and inhibition of KHS1 blocks TNF $\alpha$ -induced SAPK activation but not NF $\kappa$ B activation. The mechanism by which TRAF2 activates KHS1 is not known. Cotransfection of TRAF2- and KHS1- 15           expressing constructs in 293T cells failed to reveal a direct association between these two molecules. KHS1 activates the SAPK pathway by a direct association with the constitutively active kinase MEKK1. MEKK1 subsequently activates SEK1, which in turn activates SAPK. Neither the MAPK nor the p38 kinase pathways are activated by KHS1 (Shi, C-S and Kehrl. J.H. (1997) J. Biol. Chem. 272, 32102-32107). In addition to its catalytic domain, downstream 20           25           30

signaling of KHS1 requires its conserved C-terminus (Diener, K. et al (1997) Proc. Natl. Acad. Sci. 94, 9687-9692).

GCK (germinal center kinase) is a constitutively active 97,000 dalton STK that is broadly expressed. GCK may participate in B-cell differentiation since its expression is localized to the germinal center within lymphoid follicles. GCK activates the SAPK pathway in response to TNF $\alpha$  via activation of SEK1. The upstream activators of GCK in response to cytokines as well as the immediate downstream target of this kinase are unknown. The C-terminus of GCK is sufficient to activate SEK1 (Pombo, C.M. et al (1995) Nature, 377, 750-754).

The murine orthologue of GCK, rab8ip (rab8-interacting protein), is a 97,000 dalton protein that fractionates with both the soluble cytoplasmic fraction as well as with a salt-sensitive fraction associated with the basolateral membrane of the trans-Golgi region in polarized MDCK epithelial cells. The C-terminus of rab8ip binds to rab8, a small GTP-binding protein required for vesicular transport from the Golgi apparatus (Ren, M. et al. (1996) Proc. Natl. Acad. Sci. 93, 5151-5155). In addition to inducing the transcriptional activation of cytokines like IL2 via SAPK, GCK may also promote the rab-dependent release of secretory proteins in response to TNF $\alpha$  (Buccione, R. et al (1995) Mol. Bio. Cell 6, 291).

HPK1 (hematopoietic protein kinase) is a constitutively active 90,000 dalton STK restricted to hematopoietic cells. HPK1 activates the SAPK pathway by directly binding to and activating MEKK1 (Hu, M. et al (1996) Genes and Dev. 10:2251-2264) as well as the ubiquitously expressed mixed-lineage kinase MLK-3 (Kiefer, F. et al (1996) EMBO J. 15:7013-7025). This function of HPK1 requires, in contrast to GCK, both its kinase domain as

well as its C-terminus. The upstream activators of HPK1 remain unknown. HPK1 also plays a key role as a mediator of transforming growth factor- $\beta$  (TGF $\beta$ ) signaling. HPK1 activates the TGF $\beta$ -activated kinase (TAK), which in turn stimulates the SAPK pathway by phosphorylating SEK1 (Wang W. et al (1997) J. Biol. Chem. 272:22771-22775).

KHS2 is expressed in thymus, dendrocytes and monocytes.

KHS2 could have a complementary function to that of KHS1 as a mediator of SAPK activation in the cellular response to inflammatory cytokines. KHS2 could have the potential to interact directly with TRAF2 since a STK with the predicted molecular weight of KHS2 (approximately 101,000 daltons) is found in the TNFR-TRAF2 complex upon TNF $\alpha$  stimulation (VanArsdale, T. and Ware, C.F. (1994) J. Immunol. 153, 3043-3050). The presence of a putative binding domain for Rab or a Rab-like molecule at the C-terminus of KHS2 indicates that KHS2, in addition to having a potential role in the TRAF2-dependant TNF $\alpha$  cytokine response, could also mediate signaling events that utilize small GTPase proteins. Alternatively, the binding of a small GTPase protein to the C-terminus of KHS2 may be required for its potential TRAF2-dependant signaling to a downstream kinase such as MEKK1.

#### Human GEK2, SULU1 and SULU3

A recent report (Y-W Qian et al., Science 282:1701-1704,1998) described xPlkk1 as the activator of Plx1 (the *Xenopus* Polo kinase). In *Xenopus* oocytes, the STK Plkk1 can phosphorylate and activate Plx1 STK (the mammalian Polo kinase or PLK). A dominant-negative (kinase-dead) form of xPlkk1 prevents Plx1 activation and delays germinal vesicle breakdown. Yet another unidentified kinase is probably responsible for xPlkk1 activation during mitosis.



The homology through the entire length of the xPlkk1 protein with GEK2 suggests that GEK2 might represent the human homologue for xPlkk1. Based on this, GEK2 might be upstream of PLK in mammalian cells. In addition, based on the phage display screen results using the SULU1 coiled-coil2 domain as bait, SULU1 might also interact in vivo with GEK2 and therefore regulate GEK2 (and/or SLK through the coiled-coil domain) activation leading to PLK activation and mitosis.

If such a cascade of events is required for mitosis in mammalian cells, interruption of this signaling cascade at any point might block mitosis and could be beneficial for cancer treatment.

A recently cloned STE20-subfamily kinase, rat TAO1, is most likely the rodent orthologue of human SULU3 (Hutchinson, M. et al. J. Biol. Chem 273:28625-28632, 1998). TAO1 activates MEK3, 4 and 6 in vitro, while in transfected cells it associates and activates only MEK3, resulting in phosphorylation and activation of p38. These results implicate TAO1 (SULU3) in the regulation of the p38 containing stress-responsive MAP kinase pathway.

Human SULU1 is weakly expressed in hematopoietic sources whereas SULU3 is found in B-cells and TH1-restricted T cells. These mammalian SULU STKs display strong homology to the *C. elegans* SULU kinase. The role that this kinase plays in nematode development is unknown. The strong sequence homology between the catalytic domain of mammalian SULU kinases and other STE20-subfamily kinases such as SOK-1 (human STE20) and KHS2 suggests that the mammalian kinases may participate in the stress-response pathway. The potential coiled-coil domains found at the C-terminus of the SULU kinases may play a role in the regulation of this kinase.

Murine LOK (lymphocyte-oriented kinase) is a constitutively activated STK of approximately 130,000 daltons that is predominantly expressed in spleen, thymus and bone marrow (Kuramochi, S. et al (1997) J. Biol. Chem. 272: 22679-22684) as well as in meiotic testicular and primordial germ cells. The LOK1 gene is located in chromosome 11 of the mouse near the *wr* locus, a region that is associated with reproductive and neurological defects (Yanagisawa, M. et al (1996) Mol. Reprod. and Dev. 45:411-420). LOK does not activate any of the known MAPK pathways (ERK, JNK and p38) nor the NFkB pathway. The upstream signaling elements of LOK as well as the extracellular stimuli that utilize this kinase to elicit a biological response are also unknown (Kuramochi, S. et al (1997) J. Biol. Chem. 272: 22679-22684).

Human GEK2 is highly related to murine LOK, but based on sequence divergence in the non-catalytic domain, it appears to be a distinct member of this STE20-subfamily. GEK2 may signal through a pathway that remains to be defined. The presence of potential coiled-coil regions at the C-terminus of GEK2 could play a key role in regulating the functions of this kinase.

#### Human PAK4 and PAK5

The p21 activated protein kinases (PAK) are a closely related subgroup of the STE20 family of serine/threonine kinases. Extensive genetic and biochemical analysis of the budding yeast STE20 has shown the critical role this serine/threonine kinase plays at the juncture of several important intracellular pathways required to appropriately respond to extracellular signals. STE20 links the transcriptional response by mediating the activation of the appropriate downstream MAPK pathway as well as coupling

changes in cellular morphology via its control of the actin cytoskeleton.

A hallmark of the PAK subgroup is their small G protein-binding domain (PBD) that confers G protein-dependent activation upon this group of kinases. Via the PBD, PAKs bind to activated small G proteins resulting in the derepression of the PAK's intrinsic kinase activity.

Until recently, there were three known PAK kinases: PAK1, a 68 kD protein whose expression is restricted expression to brain, muscle, and spleen; PAK2 (PAK1, PAK65), a 62 kD protein whose expression is ubiquitous; and PAK3, a 65kD protein whose expression is restricted to the brain. Similar to STE20, the mammalian PAKs (1,2, and 3) have been shown to respond to extracellular signals (growth factors, mitogens, cytokines and a variety of cellular stresses) (Bagrodia, et al. (1995). J. Biol. Chem. 270: 22731-22737; Zhang, S., et al. (1995). J. Biol. Chem. 270: 23934-23936, Frost, J. et al. (1998) J. Biol. Chem. 273: 28191-28198; Galisteo, M. et al. (1996) J. Biol. Chem. 271: 20997-21000), and are linked to TCR activation (Yablonski, D., et al. (1998) EMBO J. 17: 5647-5657), and heterotrimeric G protein-coupled receptors (Knaus, U. et al. (1995) Science 269: 221-223).

The PAKs were originally identified as effectors for members of the Rho family of small G proteins (such as Rac and Cdc42), hence their name, p21-activated kinases (PAK) (Manser et al Nature 367:40-46). The recruitment of the PAKs to the appropriate intracellular location is critical to their function. Attempts to elucidate the role played by PAKs in intracellular signaling and morphological changes is complicated due to the complex interactions by which they can be recruited by such factors as activated small G

proteins (rac, cdc42), adaptors (nck) and exchange proteins (PIX, Cool).

The adaptor molecule, Nck, is constitutively bound via its SH3 domain to the proline-rich motif in the N-terminal portion of PAK1. Binding of the Nck-PAK complex to activated growth factor receptors in response to growth factor stimulation provides a mechanism to link growth factor-stimulated and stress-response pathways (Galisteo, M. et al. (1996) J. Biol. Chem. 271:20997-21000).

The PBD found at the N-terminus of PAK1 is responsible for its high-affinity interaction with the GTP-bound forms of Cdc42 and Rac (Burbelo, P. et al. (1995) J. Biol. Chem. 270:29071-29074). The exact mechanism through which the small GTPases activate PAKs may involve, in part, association of the kinase with activated growth factor receptors through guanine nucleotide exchange factors (GEFs). GEFs activate small GTPases by catalyzing the formation of their GTP-bound state, thereby promoting their association with, and activation of, PAKs. The known mammalian PAK kinases, as well as *Drosophila* and *C. elegans* PAKs, all conserve an N-terminal extracatalytic motif responsible for a high-affinity interaction with the GEF, PIX. The PAK-Cdc42 interaction and subsequent PAKs occurs as a PIX/PAK complex (Manser, E. et al. (1998) Molecular Cell, 1, 183-192).

PAK signaling stimulated by heterotrimeric G proteins is mediated through the interaction between a short conserved amino acid region located at the C-terminus of PAK1 with the G-protein  $\beta$ -subunit (Leeuw, T. et al. (1998) Nature, 391: 191-195).

A variety of studies have indicated that the human PAKs are involved in mediating the activation of stress-activated protein kinase pathways (JNK and to lesser extent p38).

PAKs are also potential mediators in the crosstalk between the pathways regulated by the Rho family of small G proteins and the signaling pathways directly downstream of Ras leading to the activation of the ERK pathway (Bagrodia, et al. (1995). J. Biol. Chem. 270: 22731-22737; Zhang, S., et al. (1995). J. Biol. Chem. 270: 23934-23936; Brown, J., et al. (1996) Curr Biol. 6:598-60596; Frost, J., et al. (1996). Mol. Cell. Biol. 16: 3707-3713).

PAK1 has been implicated in phosphorylating a regulatory site in MEK1 that is necessary for MEK1's ability to interact with Raf1 (Frost, et al. (1997) EMBO J. 16:6426-6438). PAK3 has been shown to phosphorylate Raf1 on a site that is important for Raf1 activity (King, A., et al. (1998). Nature 396: 180-183).

PAKs play an important role in controlling morphological changes in cell shape mediated by the actin cytoskeleton. Such morphological changes are required for cellular functions ranging from cell division and proliferation to cell motility and vesicle transport. PAK activity has been implicated in the localized assembly (leading edge) and disassembly (retracting edge) of focal adhesions necessary for cell motility (Frost J. et al (1998) J. Biol. Chem. 273:28191-28198).

PAK2 may have a role in the morphological changes induced during apoptosis (Membrane and morphological changes in apoptotic cells regulated by caspase-mediated activation of PAK2. (Rudel, T. (1997) Science. 276:1571-4)), and PAK1 may be important in preventing apoptosis (Faure S, et al. (1997) EMBO J. (1997) 16:5550-61). In addition to overcoming mitogen- and anchorage-independent growth, tumor cells need to escape the programmed cell death that accompanies deregulated cell growth. Thus, inhibition of PAKs may be effective in triggering apoptosis in tumors.

A direct requirement for PAKs in the transformation of mammalian cells has been shown for PAK1 and PAK2. Kinase-dead alleles of PAK1 block ras transformation of RAT1 and Schwann cells (Tang, Y., et al. (1997) Mol. Cell. Biol. 17, 4454-4464). Dominant-negative alleles of PAK2 have been shown to interfere with ras-mediated transformation of mammalian cells (Osada, S., (1997) FEBS Lett 404:227-233)

Mutations in PAK3 have been implicated in nonsyndromic X-linked mental retardation suggesting a role for PAK3 in cognitive function (Allen, K. et al. (1998) Nat. Genet. 20: 25-30). PAK1 has been implicated in neurite outgrowth in PC12 cells (Daniels, R. et al. (1998) EMBO J. 17: 754-764; Nikolic, M. et al. (1998) Nature 395:194-198).

Finally, PAK-like STKs may also play a role in AIDS pathogenesis since the myristoylated 27kD membrane-associated HIV Nef gene product directly interacts with and activates these kinases via cdc42 and Rac. The Nef-mediated activation of PAK-like STKs correlates with the induction of high viral titers and the development of AIDS in infected hosts (Cullen, B. R. (1996) Curr. Biol. 6:1557-1559).

Our results show that PAK4 is expressed in thymus, dendrocytes, mast cells, monocytes, as well as in T cells (TH2-restricted cells and MOLT4) and the B cell line RPMI. PAK5 is found in mast cells and in the T cell line MOLT4. These data suggest potential roles for PAK4 and PAK5 in the immune system.

PAK4 and PAK5 share with the known PAKs a potential cdc42-binding motif at their N-termini. Both PAK4 and PAK5 display sequence homology in their C-termini to a motif responsible for an interaction between PAK1 and the  $\beta$ -subunit of heterotrimeric G-proteins (amino acid residues 665-676 in PAK 4, and amino acid residues 386-398 in PAK5). Consequently, PAK4, and possibly PAK5, could mediate

signaling events originating from growth factors as well as from ligands that stimulate G-protein-linked receptors.

PAK4 conserves a leucine (leu 44), that when mutated to a phenylalanine renders the kinase activity of human PAK1 constitutively active, bypassing its cdc42-binding requirement for activation (Brown J. et al (1996) Current Biol. 6:598-605). PAK5 contains an isoleucine at the equivalent position. Therefore, the mechanism by which cdc42 potentially activates human PAK1, PAK4, and possibly PAK5, may be very similar.

PAK4 and PAK5 however, lack the PIX-binding motif, and consequently cdc42-activating GEFs other than PIX (for example Dbp and Cdc25) must be responsible for the activation of these kinases. Alternatively, PAK4 and PAK5 may be activated by another GTPase, such as Rac1 which uses the Tiam1 GEF for its activation to the GTP-bound state.

PAK4 and PAK5 also lack the PxxP motif responsible for the Nck-PAK1 association. Between the PBD or cdc42-binding N-terminal motifs and the putative GEF-binding regions, PAK4 and PAK5 have long insertions (185 and 123 amino acids for PAK4 and PAK5, respectively) relative to PAK1. This region probably confers different binding characteristics to adaptor molecules and/or GEFs from those exhibited by known mammalian PAKs.

PAKs have been shown to be upstream in pathways leading to activation of both the JNK (Bagrodia, S., et al. (1995) J. Biol. Chem. 270: 22731-22737) and ERK kinase pathways (Brown, J., et al. (1996). Curr Biol. 6:598-605). PAK1 was shown to synergize with ras in activation of the ERK pathway through phosphorylation of MEK1 (Frost, J. et al. (1997). EMBO J. 16:6426-6438). Our data shows that MEK1 serves as an *in vitro* substrate for PAK4, suggesting a potential role

for PAK4 in the activation of the ERK pathway and mitogenesis.

PAK5 may also have a mitogenic role, and be linked to cancer, based on its expression profile (elevated RNA and protein levels in a wide variety of tumor cell lines), its interaction with cdc42 via its PBD, and the ability of a kinase-dead allele (Lys350, 351 Ala) to block ras transformation of NIH3T3 cells. Thus, a screen for small molecule inhibitors of PAK5 kinase activity may yield compounds with therapeutic potential for intervention in cancer derived from a wide variety of tissue types.

PAK4 and PAK5 may also play a role in HIV pathogenesis as potential mediators of Nef signaling, since none of the known PAKs correspond to the PAK-like kinase shown to interact with, and be activated by, the HIV nef protein (Lu, X. et al. (1996) Current Biology 6:1677-1684)

The 3' untranslated region of PAK4 contains a CA repeat that is prone to undergo expansion. CA dinucleotide repeat instability has been associated with disease (Toren, M.Z. et al (1998) Am. J. Hematol. 57: 148-152), and expansion of such repeat in the 3' untranslated region of PAK4 could implicate this kinase in as yet unknown pathologies.

#### Clinical applications

Human STLK2, STLK3, STLK4, STLK5, STLK6, and STLK7

STLK3, STLK5, STLK6 and STLK7, as well as other homologues of the STLK subfamily of STE20 protein kinases such as STLK4, may play an important role as mediators of the immune response. Thus, they are targets for the development of specific small molecule inhibitors to treat immunological diseases, including, but not limited to, rheumatoid arthritis, chronic inflammatory bowel diseases (e.g. Crohn's disease), chronic inflammatory pelvic disease,



multiple sclerosis, asthma, osteoarthritis, psoriasis, atherosclerosis, rhinitis and autoimmunity, as well as in organ transplantation. Other diseases include cardiovascular diseases.

5           The human STLKs may also play an important role in cell growth regulation. Thus, they are targets for developing small molecule kinase inhibitors for the treatment of cancer and metastases. STLK5 maps to a chromosomal region frequently amplified in a variety of tumors including those  
10       from non-small cell lung cancer, breast cancer and peripheral nerve tumors. This suggests that STLK5 could play a role in the development, maintenance, or progression of human tumors.

          The potential role of human STLKs 2,3, and 4 in  
15       mediating oxidative stress strongly suggests that drugs targeting these kinases could prove useful in the treatment of myocardial infarction, arrhythmia and other cardiomyopathies, stroke, renal failure, oxidative stress-related neurodegenerative disorders such amyotrophic lateral  
20       sclerosis, Parkinson's disease and Leigh syndrome, a necrotizing mitochondrial encephalopathy, as well.

#### Human ZC1, ZC2, ZC3, and ZC4

          ZC1 may be a component of the CD28-signaling pathway  
25       and therefore important in T cell activation. As such, ZC1 as well as other ZC subfamily kinases, are targets for the development of specific small molecule inhibitors to treat immunological diseases, including, but not limited to, rheumatoid arthritis, chronic inflammatory bowel diseases  
30       (e.g. Crohn's disease), chronic inflammatory pelvic disease, multiple sclerosis, asthma, osteoarthritis, psoriasis, atherosclerosis, rhinitis and autoimmunity, as well as organ

transplantation. Other diseases include cardiovascular diseases.

5 ZC1 and ZC2 are also implicated in cell growth regulation. Thus, ZC subfamily kinases are targets for developing small molecule inhibitors for the treatment of cancer and metastases. ZC2 maps to a chromosomal region frequently amplified in a variety of tumors including those from non-small cell lung cancer, small cell lung cancer, and cervical cancer. This suggests that ZC2 could play a role  
10 in the development, maintenance, or progression of human tumors.

The role of human ZC1, ZC2, ZC3, and ZC4 in the inflammatory and stress-response pathways, strongly suggests that drugs targeting these kinases could have strong  
15 immunosuppressive actions. These drugs can prove valuable for the treatment of rheumatoid arthritis, atherosclerosis, autoimmune disorders and organ transplantation among others.

At least one very important class of immunosuppressants, corticosteroids, functions by blocking SAPK activation at an  
20 as yet undefined site on this pathway (Swanek, J.L. et al (1997) Mol. Cell. Biol. (1997) 6274-6282). Other immunosuppressive drugs like the pyridinyl imidazoles specifically target the p38 kinases (Kumar, S. et al (1997) Biochem. Biophys. Res. Commun. 235: 533-528). Drug  
25 targeting of the MAPK and p38 pathways could lead to the development of novel immunosuppressants.

#### Human SULU and GEK

The potential role of these novel STE20-related protein  
30 kinases in the control of mitosis strongly suggests that agents that specifically inhibit these kinases could be useful for cancer and metastases treatment.

The close homology of human STLK5, GEK2, SULU1 and SULU3 to STE20-subfamily kinases involved in the stress and oxidative response pathway strongly suggests that drugs targeting these kinases may also be useful as immunosuppressants as well as to treat ischemic disorders.

#### Human KHS2

The role of human KHS2 in the inflammatory and stress-response pathways, strongly suggests that drugs targeting this and related kinases could have strong immunosuppressive actions. These drugs can prove valuable for the treatment of rheumatoid arthritis, arteriosclerosis, autoimmune disorders and organ transplantation among others. At least one very important class of immunosuppressants, corticosteroids, functions by blocking SAPK activation at an as yet undefined site on this pathway (Swanek, J.L. et al (1997) Mol. Cell. Biol. (1997) 6274-6282). Other immunosuppressive drugs like the pyridinyl imidazoles specifically target the p38 kinases (Kumar, S. et al (1997) Biochem. Biophys. Res. Commun. 235: 533-528). Drug targeting of the MAPK and p38 pathways could lead to the development of novel immunosuppressants.

#### Human PAK family

PAK5 has a role in cancer based on its expression profile (elevated RNA and protein levels in wide variety of tumor lines), its interaction with Cdc42 via its PBD, and the ability of the kinase-dead allele of PAK5 (Lys350, 351Ala) to block ras transformation of NIH3T3 cells. Thus, a screen for small molecule inhibitors of PAK5 kinase activity may yield compounds with therapeutic potential for intervention in cancers and metastases derived from a wide range of tissue types.

PAK5 maps to a chromosomal region frequently amplified in a variety of tumors including those from non-small cell lung cancer, and small cell lung cancer. These findings suggest that PAK5 could play a role in the development, maintenance, or progression of human tumors and/or metastases.

The role of human PAK4, and PAK5 in the inflammatory and stress-response pathways also strongly suggests that drugs targeting these kinases could have strong immunosuppressive actions. These drugs can prove valuable for the treatment of rheumatoid arthritis, atherosclerosis, autoimmune disorders and organ transplantation among others.

At least one very important class of immunosuppressants, corticosteroids, functions by blocking SAPK activation at an as yet undefined site on this pathway (Swanek, J.L. et al (1997) Mol. Cell. Biol. (1997) 6274-6282). Other immunosuppressive drugs like the pyridinyl imidazoles specifically target the p38 kinases (Kumar, S. et al (1997) Biochem. Biophys. Res. Commun. 235: 533-528). Drug targeting of the MAPK and p38 pathways could lead to the development of novel immunosuppressants. In addition, drugs targeting PAK4 or PAK5 could prove useful as immunosuppressants as well as in AIDS treatment.

#### VIII. Transgenic Animals.

A variety of methods are available for the production of transgenic animals associated with this invention. DNA can be injected into the pronucleus of a fertilized egg before fusion of the male and female pronuclei, or injected into the nucleus of an embryonic cell (e.g., the nucleus of a two-cell embryo) following the initiation of cell division (Brinster et al., Proc. Nat. Acad. Sci. USA 82: 4438-4442, 1985). Embryos can be infected with viruses, especially

retroviruses, modified to carry inorganic-ion receptor nucleotide sequences of the invention.

Pluripotent stem cells derived from the inner cell mass of the embryo and stabilized in culture can be manipulated in culture to incorporate nucleotide sequences of the invention. A transgenic animal can be produced from such cells through implantation into a blastocyst that is implanted into a foster mother and allowed to come to term.

Animals suitable for transgenic experiments can be obtained from standard commercial sources such as Charles River (Wilmington, MA), Taconic (Germantown, NY), Harlan Sprague Dawley (Indianapolis, IN), etc.

The procedures for manipulation of the rodent embryo and for microinjection of DNA into the pronucleus of the zygote are well known to those of ordinary skill in the art (Hogan et al., supra). Microinjection procedures for fish, amphibian eggs and birds are detailed in Houdebine and Chourrout (Experientia 47: 897-905, 1991). Other procedures for introduction of DNA into tissues of animals are described in U.S. Patent No., 4,945,050 (Sandford et al., July 30, 1990).

By way of example only, to prepare a transgenic mouse, female mice are induced to superovulate. Females are placed with males, and the mated females are sacrificed by CO<sub>2</sub> asphyxiation or cervical dislocation and embryos are recovered from excised oviducts. Surrounding cumulus cells are removed. Pronuclear embryos are then washed and stored until the time of injection. Randomly cycling adult female mice are paired with vasectomized males. Recipient females are mated at the same time as donor females. Embryos then are transferred surgically. The procedure for generating transgenic rats is similar to that of mice (Hammer et al., Cell 63:1099-1112, 1990).

Methods for the culturing of embryonic stem (ES) cells and the subsequent production of transgenic animals by the introduction of DNA into ES cells using methods such as electroporation, calcium phosphate/DNA precipitation and direct injection also are well known to those of ordinary skill in the art (Teratocarcinomas and Embryonic Stem Cells, A Practical Approach, E.J. Robertson, ed., IRL Press, 1987).

In cases involving random gene integration, a clone containing the sequence(s) of the invention is co-transfected with a gene encoding resistance. Alternatively, the gene encoding neomycin resistance is physically linked to the sequence(s) of the invention. Transfection and isolation of desired clones are carried out by any one of several methods well known to those of ordinary skill in the art (E.J. Robertson, *supra*).

DNA molecules introduced into ES cells can also be integrated into the chromosome through the process of homologous recombination (Capecchi, *Science* 244: 1288-1292, 1989). Methods for positive selection of the recombination event (*i.e.*, neo resistance) and dual positive-negative selection (*i.e.*, neo resistance and gancyclovir resistance) and the subsequent identification of the desired clones by PCR have been described by Capecchi, *supra* and Joyner *et al.* (*Nature* 338: 153-156, 1989), the teachings of which are incorporated herein in their entirety including any drawings. The final phase of the procedure is to inject targeted ES cells into blastocysts and to transfer the blastocysts into pseudopregnant females. The resulting chimeric animals are bred and the offspring are analyzed by Southern blotting to identify individuals that carry the transgene. Procedures for the production of non-rodent mammals and other animals have been discussed by others (Houdebine and Chourrout, *supra*; Pursel *et al.*, *Science*

244:1281-1288, 1989; and Simms et al., Bio/Technology 6:179-183, 1988).

Thus, the invention provides transgenic, nonhuman mammals containing a transgene encoding a kinase of the invention or a gene effecting the expression of the kinase. Such transgenic nonhuman mammals are particularly useful as an *in vivo* test system for studying the effects of introduction of a kinase, or regulating the expression of a kinase (i.e., through the introduction of additional genes, antisense nucleic acids, or ribozymes).

A "transgenic animal" is an animal having cells that contain DNA which has been artificially inserted into a cell, which DNA becomes part of the genome of the animal which develops from that cell. Preferred transgenic animals are primates, mice, rats, cows, pigs, horses, goats, sheep, dogs and cats. The transgenic DNA may encode human STE20-related kinases. Native expression in an animal may be reduced by providing an amount of anti-sense RNA or DNA effective to reduce expression of the receptor.

#### IX. Gene Therapy

STE20-related kinases or their genetic sequences will also be useful in gene therapy (reviewed in Miller, Nature 357:455-460, 1992). Miller states that advances have resulted in practical approaches to human gene therapy that have demonstrated positive initial results. The basic science of gene therapy is described in Mulligan (Science 260:926-931, 1993).

In one preferred embodiment, an expression vector containing STE20-related kinase coding sequence is inserted into cells, the cells are grown *in vitro* and then infused in large numbers into patients. In another preferred embodiment, a DNA segment containing a promoter of choice (for

example a strong promoter) is transferred into cells containing an endogenous gene encoding kinases of the invention in such a manner that the promoter segment enhances expression of the endogenous kinase gene (for  
5 example, the promoter segment is transferred to the cell such that it becomes directly linked to the endogenous kinase gene).

The gene therapy may involve the use of an adenovirus containing kinase cDNA targeted to a tumor, systemic kinase  
10 increase by implantation of engineered cells, injection with kinase-encoding virus, or injection of naked kinase DNA into appropriate tissues.

Target cell populations may be modified by introducing altered forms of one or more components of the protein  
15 complexes in order to modulate the activity of such complexes. For example, by reducing or inhibiting a complex component activity within target cells, an abnormal signal transduction event(s) leading to a condition may be decreased, inhibited, or reversed. Deletion or missense  
20 mutants of a component, that retain the ability to interact with other components of the protein complexes but cannot function in signal transduction may be used to inhibit an abnormal, deleterious signal transduction event.

Expression vectors derived from viruses such as  
25 retroviruses, vaccinia virus, adenovirus, adeno-associated virus, herpes viruses, several RNA viruses, or bovine papilloma virus, may be used for delivery of nucleotide sequences (e.g., cDNA) encoding recombinant kinase of the invention protein into the targeted cell population (e.g.,  
30 tumor cells). Methods which are well known to those skilled in the art can be used to construct recombinant viral vectors containing coding sequences (Maniatis et al., Molecular Cloning: A Laboratory Manual, Cold Spring Harbor



Laboratory, N.Y., 1989; Ausubel et al., Current Protocols in Molecular Biology, Greene Publishing Associates and Wiley Interscience, N.Y., 1989). Alternatively, recombinant nucleic acid molecules encoding protein sequences can be  
5 used as naked DNA or in a reconstituted system e.g., liposomes or other lipid systems for delivery to target cells (e.g., Felgner et al., Nature 337:387-8, 1989). Several other methods for the direct transfer of plasmid DNA into  
10 cells exist for use in human gene therapy and involve targeting the DNA to receptors on cells by complexing the plasmid DNA to proteins (Miller, supra).

In its simplest form, gene transfer can be performed by simply injecting minute amounts of DNA into the nucleus of a cell, through a process of microinjection (Capecchi, Cell  
15 22:479-88, 1980). Once recombinant genes are introduced into a cell, they can be recognized by the cell's normal mechanisms for transcription and translation, and a gene product will be expressed. Other methods have also been attempted for introducing DNA into larger numbers of cells.

20 These methods include: transfection, wherein DNA is precipitated with  $\text{CaPO}_4$  and taken into cells by pinocytosis (Chen et al., Mol. Cell Biol. 7:2745-52, 1987); electroporation, wherein cells are exposed to large voltage pulses to introduce holes into the membrane (Chu et al.,  
25 Nucleic Acids Res. 15:1311-26, 1987); lipofection/liposome fusion, wherein DNA is packaged into lipophilic vesicles which fuse with a target cell (Felgner et al., Proc. Natl. Acad. Sci. USA. 84:7413-7417, 1987); and particle  
30 bombardment using DNA bound to small projectiles (Yang et al., Proc. Natl. Acad. Sci. 87:9568-9572, 1990). Another method for introducing DNA into cells is to couple the DNA to chemically modified proteins.

It has also been shown that adenovirus proteins are capable of destabilizing endosomes and enhancing the uptake of DNA into cells. The admixture of adenovirus to solutions containing DNA complexes, or the binding of DNA to polylysine covalently attached to adenovirus using protein crosslinking agents substantially improves the uptake and expression of the recombinant gene (Curiel et al., Am. J. Respir. Cell. Mol. Biol., 6:247-52, 1992).

As used herein "gene transfer" means the process of introducing a foreign nucleic acid molecule into a cell. Gene transfer is commonly performed to enable the expression of a particular product encoded by the gene. The product may include a protein, polypeptide, anti-sense DNA or RNA, or enzymatically active RNA. Gene transfer can be performed in cultured cells or by direct administration into animals.

Generally gene transfer involves the process of nucleic acid contact with a target cell by non-specific or receptor mediated interactions, uptake of nucleic acid into the cell through the membrane or by endocytosis, and release of nucleic acid into the cytoplasm from the plasma membrane or endosome. Expression may require, in addition, movement of the nucleic acid into the nucleus of the cell and binding to appropriate nuclear factors for transcription.

As used herein "gene therapy" is a form of gene transfer and is included within the definition of gene transfer as used herein and specifically refers to gene transfer to express a therapeutic product from a cell *in vivo* or *in vitro*. Gene transfer can be performed *ex vivo* on cells which are then transplanted into a patient, or can be performed by direct administration of the nucleic acid or nucleic acid-protein complex into the patient.

In another preferred embodiment, a vector having nucleic acid sequences encoding a STE20-related kinase

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polypeptide is provided in which the nucleic acid sequence is expressed only in specific tissue. Methods of achieving tissue-specific gene expression are set forth in International Publication No. WO 93/09236, filed November 3, 1992 and published May 13, 1993.

In all of the preceding vectors set forth above, a further aspect of the invention is that the nucleic acid sequence contained in the vector may include additions, deletions or modifications to some or all of the sequence of the nucleic acid, as defined above.

In another preferred embodiment, a method of gene replacement is set forth. "Gene replacement" as used herein means supplying a nucleic acid sequence which is capable of being expressed *in vivo* in an animal and thereby providing or augmenting the function of an endogenous gene which is missing or defective in the animal.

#### X. Administration of Substances

Methods of determining the dosages of compounds to be administered to a patient and modes of administering compounds to an organism are disclosed in U.S. Application Serial No. 08/702,282, filed August 23, 1996 and International patent publication number WO 96/22976, published August 1 1996, both of which are incorporated herein by reference in their entirety, including any drawings, figures, or tables. Those skilled in the art will appreciate that such descriptions are applicable to the present invention and can be easily adapted to it.

The proper dosage depends on various factors such as the type of disease being treated, the particular composition being used, and the size and physiological condition of the patient. Therapeutically effective doses for the compounds described herein can be estimated initially from

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cell culture and animal models. For example, a dose can be formulated in animal models to achieve a circulating concentration range that initially takes into account the  $IC_{50}$  as determined in cell culture assays. The animal model data can be used to more accurately determine useful doses in humans.

Plasma half-life and biodistribution of the drug and metabolites in the plasma, tumors, and major organs can be also be determined to facilitate the selection of drugs most appropriate to inhibit a disorder. Such measurements can be carried out. For example, HPLC analysis can be performed on the plasma of animals treated with the drug and the location of radiolabeled compounds can be determined using detection methods such as X-ray, CAT scan, and MRI. Compounds that show potent inhibitory activity in the screening assays, but have poor pharmacokinetic characteristics, can be optimized by altering the chemical structure and retesting. In this regard, compounds displaying good pharmacokinetic characteristics can be used as a model.

Toxicity studies can also be carried out by measuring the blood cell composition. For example, toxicity studies can be carried out in a suitable animal model as follows: 1) the compound is administered to mice (an untreated control mouse should also be used); 2) blood samples are periodically obtained via the tail vein from one mouse in each treatment group; and 3) the samples are analyzed for red and white blood cell counts, blood cell composition, and the percent of lymphocytes versus polymorphonuclear cells. A comparison of results for each dosing regime with the controls indicates if toxicity is present.

At the termination of each toxicity study, further studies can be carried out by sacrificing the animals (preferably, in accordance with the American Veterinary

Medical Association guidelines Report of the American Veterinary Medical Assoc. Panel on Euthanasia, *Journal of American Veterinary Medical Assoc.*, 202:229-249, 1993).

Representative animals from each treatment group can then be  
5 examined by gross necropsy for immediate evidence of  
metastasis, unusual illness, or toxicity. Gross  
abnormalities in tissue are noted, and tissues are examined  
histologically. Compounds causing a reduction in body  
weight or blood components are less preferred, as are  
10 compounds having an adverse effect on major organs. In  
general, the greater the adverse effect the less preferred  
the compound.

For the treatment of cancers the expected daily dose of  
a hydrophobic pharmaceutical agent is between 1 to 500  
15 mg/day, preferably 1 to 250 mg/day, and most preferably 1 to  
50 mg/day. Drugs can be delivered less frequently provided  
plasma levels of the active moiety are sufficient to  
maintain therapeutic effectiveness.

Plasma levels should reflect the potency of the drug.  
20 Generally, the more potent the compound the lower the plasma  
levels necessary to achieve efficacy.

#### EXAMPLES

The examples below are not limiting and are merely  
25 representative of various aspects and features of the  
present invention. The examples below demonstrate the  
isolation and characterization of the STE20-related kinases  
of the invention.

EXAMPLE 1: Isolation of cDNAs Encoding Mammalian  
STE20-related Protein Kinases

Materials and Methods

Identification of novel clones

5           Total RNAs were isolated using the Guanidine  
Salts/Phenol extraction protocol of Chomczynski and Sacchi  
(P. Chomczynski and N. Sacchi, Anal. Biochem. 162, 156  
(1987)) from primary human tumors, normal and tumor cell  
lines, normal human tissues, and sorted human hematopoietic  
10       cells. These RNAs were used to generate single-stranded  
cDNA using the Superscript Preamplification System (GIBCO  
BRL, Gaithersburg, MD; Gerard, GF et al. (1989), FOCUS 11,  
66) under conditions recommended by the manufacturer. A  
typical reaction used 10 µg total RNA with 1.5 µg oligo(dT)<sub>12-</sub>  
15       <sub>18</sub> in a reaction volume of 60 µL. The product was treated  
with RNaseH and diluted to 100 µL with H<sub>2</sub>O. For subsequent  
PCR amplification, 1-4 µL of this ssDNA was used in each  
reaction.

20           Degenerate oligonucleotides were synthesized on an  
Applied Biosystems 3948 DNA synthesizer using established  
phosphoramidite chemistry, precipitated with ethanol and  
used unpurified for PCR. The sequence of some of the  
degenerate oligonucleotide primers and the amino acid motif  
they encode is as follows:

25           TRK1 5'-CTGAATTCGGNGCNTTYGGNAARGT-3' GAFGKV (sense)  
TRK4 5'-GCTGGATCCYTCNGGNGGCATCCA-3' WMPPE (antisense)  
ROS1 5'-GCNTTYGGNGARGTNTAYGARGG-3' AFGEVYEG (sense)  
CCK4b 5'-GCTGGATCCYTCNGGNSWCATCCA-3' WMSPE (antisense)  
CCK4c 5'-GAGTTYGGNGARGTNTTYTNGC-3' EFGEVYEG (sense)

30           These primers were derived from the sense and antisense  
strands of conserved motifs within the catalytic domain of  
several protein kinases. Degenerate nucleotide residue

designations are: N = A, C, G, or T; R = A or G; Y = C or T; H = A, C or T not G; D = A, G or T not C; S = C or G; and W = A or T.

5 PCR reactions were performed using degenerate primers applied to multiple single-stranded cDNAs. The primers were added at a final concentration of 5  $\mu$ M each to a mixture containing 10 mM TrisHCl, pH 8.3, 50 mM KCl, 1.5 mM MgCl<sub>2</sub>, 200  $\mu$ M each deoxynucleoside triphosphate, 0.001% gelatin, 1.5 U AmpliTaq DNA Polymerase (Perkin-Elmer/Cetus), and 1-4  
10  $\mu$ L cDNA. Following 3 min denaturation at 95 °C, the cycling conditions were 94 °C for 30 s, 50 °C for 1 min, and 72 °C for 1 min 45 s for 35 cycles. PCR fragments migrating between 300-350 bp were isolated from 2% agarose gels using the GeneClean Kit (Bio101), and T-A cloned into the pCRII vector  
15 (Invitrogen Corp. U.S.A.) according to the manufacturer's protocol.

Colonies were selected for mini plasmid DNA-preparations using Qiagen columns and the plasmid DNA was sequenced using a cycle sequencing dye-terminator kit with  
20 AmpliTaq DNA Polymerase, FS (ABI, Foster City, CA). Sequencing reaction products were run on an ABI Prism 377 DNA Sequencer, and analyzed using the BLAST alignment algorithm (Altschul, S.F. et al., J.Mol.Biol. 215: 403-10).

Additional PCR strategies were employed to connect  
25 various PCR fragments or ESTs using exact or near exact oligonucleotide primers as detailed in the results section for each cDNA. PCR conditions were as described above except the annealing temperatures were calculated for each oligo pair using the formula:  $T_m = 4(G+C) + 2(A+T)$ .

30

#### Isolation of cDNA clones:

Human cDNA libraries were probed with PCR or EST fragments corresponding to STE20-related genes. Probes were

<sup>32</sup>P-labeled by random priming and used at 2x10<sup>6</sup> cpm/mL following standard techniques for library screening. Pre-hybridization (3 h) and hybridization (overnight) were conducted at 42 °C in 5X SSC, 5X Denhart's solution, 2.5% dextran sulfate, 50 mM Na<sub>2</sub>PO<sub>4</sub>/NaHPO<sub>4</sub>, pH 7.0, 50% formamide with 100 mg/mL denatured salmon sperm DNA. Stringent washes were performed at 65 °C in 0.1X SSC and 0.1% SDS. DNA sequencing was carried out on both strands using a cycle sequencing dye-terminator kit with AmpliTaq DNA Polymerase, FS (ABI, Foster City, CA). Sequencing reaction products were run on an ABI Prism 377 DNA Sequencer.

#### Makegene Bioinformatics EST assembler

The EST reports were downloaded from ncbi ([www.ncbi.nlm.nih.gov](http://www.ncbi.nlm.nih.gov)). After uncompressing the files, the program 'report2est' was scripted to extract the following information: 1) EST names, 2) GenBank Accession numbers, 3) GenBank gi numbers, 4) Clone Id numbers, 5) the nucleotide sequences of the ESTs 6) the organism, 7) the library name, 8) the name of the lab, and 9) the institution. The output of 'report2est' is a file in FASTA format with all of the information listed above in the first line of each entry except the sequence, which is listed in the second line of each entry. The resulting file is formatted for BLAST using 'pressdb' (available as part of the ncbi tool kit).

To build a gene or part of a gene from ESTs, the program 'makegene' was developed. Input to this program is a query sequence and the organism/species for which a gene is to be built. An initial search of the formatted EST database described above is performed using BLAST (blastn).

Any results that contain warnings, such as polyA tails or other repeat elements, are eliminated from future queries. The program 'blast\_parse\_reports' was developed to extract



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the FASTA header line from the search results and the output is then filtered to extract only FASTA header lines for the desired species.

5 The initial results, having been filtered for warnings and species, go into a loop in which searches against the database are repeated until no new ESTs are found. The loop consists of the following steps: 1) when possible the names of both ends of the ESTs are extracted from the database by searching using the 'Clone Id' field or the part of the 'EST  
10 name' field before the .r or .s postscript, 2) any ESTs that have been used as queries in previous loops are removed from the current query by the program 'subtract', 3) the resulting list of ESTs is used to extract the sequences from the database by the program batch\_parse\_fasta, 4) BLAST is  
15 run against the database using each sequence, 5) the output files from BLAST containing warnings are removed, 6) the results are filtered by species, and 7) the loop is reentered if there were new ESTs found in the previous pass through the loop.

20 The ESTs chosen by 'makegene' are used as input for the program 'mpd2\_cluster' (Hide, W., Burke, J, and Davison, D. U. of Houston, unpublished) which clusters overlapping sequences. The programs 'contig' (Kerlavage, T., TIGR, unpublished), 'gde2mult' and 'gde2sing' (Smith, S.W., et  
25 al., CABIOS 10, 671-675 (1994)), are used to make an alignment and consensus sequence of the overlapping ESTs.

## RESULTS

### cdna cloning and characterization of STLK2

30 The human STLK2 cDNA sequence is composed of two overlapping EST fragments, AA191319 and W16504, that were identified using a Smith-Waterman search of the EST database with STLK1 (MST3 GB:AF024636) as a query. The complete

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sequence of both clones was determined and used to generate the full-length human STL2 sequence.

EST clone AA191319 contains a 1327 bp insert and an ORF of 1146 bp (382 amino acids). EST clone W16504 contains a 2474 bp insert (not including the poly-A tail) and an ORF of 687 bp (382 amino acids).

The full-length human STLK2 cDNA (SEQ ID NO. 1) is 3268 bp long. AA191319 spans positions 1-1327 and W16504 positions 743-3216. The overlap between these two clones exhibits 100% sequence identity. The human STLK2 cDNA contains a 1248 bp ORF flanked by a 181 bp 5' UTR (1-181) and a 1784 bp 3' UTR (1433-3216) that is followed by a 52 nucleotide polyadenylated region. A polyadenylation signal (AATAAA) is found at positions 3193-3198. The sequence flanking the first ATG conforms to the Kozak consensus for an initiating methionine, and is believed to be the translational start site for STLK2. Furthermore, human STLK2, and the related SOK-1 and MST3 proteins, conserve the amino acid sequence immediately following this presumed initiating methionine.

Several EST fragments span the complete STLK2 sequence with AA191319 at the 5' end and W16504 at the 3' end.

All searches against the public nucleic acid database (NRN) and protein database (NRP) were conducted using the Smith-Waterman gap alignment program ((Smith, TF and Waterman, MS (1981) J. Mol. Biol, 147, 195-197).) with the PAM100 matrix and gap open and extension penalties of 14:1, respectively.

### cDNA Cloning and Characterization of STLK3

A mammalian STLK3 clone, 135-31-19, was first identified from a PCR screen with the degenerate oligos, TRK1 and TRK4, applied to a ssDNA generated from adult rat

brain substantia nigra. Sequence analysis of the 457 bp insert indicated that it represented a novel member of the STE20-subfamily of STKs.

5 A Smith-Waterman search of the EST database with the rat STLK3 fragment and human STLK1 (MST3 GB:AF024636) as queries identified several overlapping ESTs spanning most of the human STLK3 cDNA sequence. A Makegene analysis generated a 3037 bp contig from approximately 44 EST sequences. Since the 3' ESTs were not commercially  
10 available, a pair of primers (5'-CACAGAAACGGTCAGATTCAC-3' and 5'-GATCAGGGTGACATCAAGGGAC-3') were derived from this region to generate PCR clone 3R21-20-6 from human fetal liver sscDNA. This clone and EST AA278967 were fully sequenced to generate the full-length STLK2 cDNA sequence.

15 AA278967 is a 837 bp EST isolated by the IMAGE consortium from cDNA made from CD20+/IgD- germinal center B cells sorted from human tonsillar cells.

PCR clone 3R21-20-6 was isolated from human fetal sscDNA and contains a 1116 bp insert, including a 1086 bp  
20 ORF encoding the 362 C-terminal amino acids of STLK3.

The full-length human STLK3 cDNA (SEQ ID NO. 2) is 3030 bp long. AA278967 spans positions 1-814 and 3R21-20-6 spans positions 464-1579. The overlap between these two clones exhibits 100% sequence identity. The remaining 1452 bp of  
25 3' UTR is derived from an assembly of multiple unconfirmed EST fragments.

The near full-length human STLK3 cDNA (SEQ ID NO.2) is 3030 bp long and consists of a 1548 bp ORF flanked by a 1476 bp 3' UTR (1550-3025) and a 5 nucleotide polyadenylated  
30 region. A polyadenylation signal (AATAAA) begins at position 3004. Since the coding region is open throughout the 5' extent of this sequence, this is apparently a partial cDNA clone lacking the N-terminal start methionine. Six

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copies of a "GGCCCC" repeat were observed in positions 21-67. Five independent ESTs (AA150838, AA286879, AA251679, AA252004, AA278967) showed the same repeat, suggesting that this sequence may be an integral region of the human STLK3 gene. Stronger evidence for this being the case is provided by the sequence of the murine orthologue of STLK3 represented by a 876 bp EST W20737.

Multiple EST fragments span the complete STLK3 sequence with AA278967 at the 5' end and AA628477 and others at the 3' end.

#### cdNA Cloning and Characterization of STLK4

The human STLK4 cDNA sequence is composed of two overlapping EST fragments, AA297759 and AA100484, that were identified using a Smith-Waterman search of the EST database with STLK1 (MST3 GB:AF024636) as a query. The complete sequence of both clones was determined and used to generate the near full-length human STLK4 sequence.

AA100484 is an IMAGE consortium cDNA clone isolated from the T-84 colonic epithelium cell line. It has an insert of 3694 bp and a coding region of 1146 bp (382 amino acids). A Smith-Waterman sequence alignment against the NRN database showed this EST to be 71.4% identical to the human STE20-like kinase (GB:X99325).

W16504 is an IMAGE consortium clone isolated from a human fetal heart cDNA library. It has an insert length of 2474 bp (not including the poly-A tail) and a coding region of 687 bp (229 amino acids). A Smith-Waterman sequence alignment of W16504 against the NRN database showed this EST to be 69.2% identical to the human STE20-like kinase (GB:X99325).

The full-length human STLK2 cDNA (SEQ ID NO. 1) is 3268 bp long. AA191319 spans positions 1-1327, and W16504

positions 743-3216. The overlap between these two clones is 585 bp long with 100% sequence identity.

AA100484 is an IMAGE consortium cDNA clone isolated from the T-84 colonic epithelium cell line. AA100484 covers the bulk of Human STLK4 with its 3694 bp, which spans positions 146-3839 of SEQ ID NO:3. A second EST, AA297759, isolated from a Jurkat T cell cDNA library, spans positions 1-271 of the human STLK4 contig. The two ESTs overlap over a 126 bp stretch that has only one nucleotide discrepancy at position 149 (G in AA297759 and T in AA100484). A T at this position was chosen for the SEQ ID NO:3 based on sequence data generated from A100484. The 5' 145 bp of human STLK4 contains three sequencing ambiguities (N's in SEQ ID NO:3) arising from sequence errors in the GenBank entry for AA297759. Three amino acid sequence ambiguities in the N-terminus of human STLK4 are present also in SEQ ID NO:7 as a consequence of the sequence inaccuracies from the EST entry.

The coding region of human STLK4 is 1242 bp long (2-1243), capable of encoding a 414 amino acid polypeptide, and is followed by a 2596 nucleotide 3' UTR (1244-3839). Human STLK4 ends in a polyadenylated stretch that has 18 adenines (3840-3857). A polyadenylation signal (AATAAA) is found between positions 3822-3827. Targeted-PCR cloning identified one rat orthologue of human STLK4, clone 135-31-19. In addition, one murine orthologue of human STLK4 was recognized in the EST database as AA117483. None of these orthologues add additional N-terminal sequence to the human STLK4.

The near full-length human STLK4 cDNA (SEQ ID NO.3) is 3857 bp long and consists of a 1242 bp ORF flanked by a 2596 bp 3' UTR (1244-3839) and an 18 nucleotide polyadenylated region. Polyadenylation signals (AATAAA) begin at positions

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2181 and 3822. Since the coding region is open throughout the 5' extent of this sequence, this is apparently a partial cDNA clone lacking the N-terminal start methionine. A near full-length murine STLK4 cDNA is represented in the 1773 bp EST AA117438. It extends an additional 21 nucleotides 5' of the human STLK4 consensus, but since its coding region is open throughout the 5' extent of the sequence, this is also probably a partial cDNA clone lacking the N-terminal start methionine.

Several EST fragments span the complete STLK3 sequence with AA297759 at the 5' end and AA100484 and others at the 3' end.

#### cDNA Cloning and Characterization of STLK5

The human STLK5 cDNA sequence is composed of four overlapping sequences, AI418298, 2R96-13-1, 3R25-45-3 and R46685. A human STLK5 clone, F07734, was first identified using a Smith-Waterman search of the EST database with SPS\_sc (U33057) as a query.

AI418298 is an IMAGE consortium cDNA clone with an 895 bp insert.

PCR clone 2R96-13-1 was isolated from human brain ssDNA using primers 5'-CTCATCTGTACACACTTCATGG and 5'-GATTCCCACACTGTAGATGTC derived from F07734. 2R96-13-1 contains a 330 bp insert and an ORF of 330 bp (110 amino acids).

EST clone R46685 was identified using a Smith-Waterman search of the EST database with the C-terminus of SPS\_sc (GB:U33057) as query. Sequence analysis of the 1047 bp insert identified this EST to contain an ORF of 285 bp (95 amino acids) encoding the C-terminus of human STLK5.

PCR clone 3R25-45-3 was isolated from human fetal brain ssDNA using primers 5'-GGCCCTCGACTACATCCACCACAT and 5'-

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CAACGAAACTAACACAGCATAAGG derived from 2R96-13-1 and R46685, respectively. 3R25-45-3 contains a 330 bp insert and an ORF of 750 bp (250 amino acids).

5 The full-length human STLK5 cDNA (SEQ ID NO:96) is 2110 bp long and consists of a 1119 bp ORF flanked by a 229 bp 5' UTR and a 762 bp 3' UTR. The sequence flanking the first ATG conforms to the Kozak consensus (*supra*) for an initiating methionine, and is believed to be the translational start site for STLK5.

10 Several EST fragments span the complete STLK5 sequence with AA297059 and F07734 at the 5' end and R46686 and F03423 and others at the 3' end.

STLK5 displays a 100% match over a 41 bp stretch (position 2-42, SEQ ID NO. 97) to a human CpG island repeat (Z61277).

15

#### cDNA Cloning and Characterization of STLK6

Human STLK6 was first identified in the translated EST database (AA219667) as a novel serine threonine kinase.

20 The partial human STLK6 cDNA (SEQ ID NO:98) is 2,001 bp long and consists of a 1,254 bp ORF flanked by a 75 bp 5' UTR and a 673 bp 3' UTR. The sequence flanking the first ATG conforms to the Kozak consensus (Kozak, M., *Nucleic Acids Res.* 15, 8125-8148 (1987)) for an initiating methionine, and is believed to be the translational start site for STLK6.

25

At the time of filing, inventors believe that STLK6 does not have any significant match in the nucleic acid database.

30

#### cDNA Cloning and Characterization of STLK7

Human STLK7 was first identified in the translated EST database (AA988954) as a novel serine threonine kinase. The

original clone was not available through public sources, so a PCR fragment amplified from the sequence of AA988954 yielded 5R54-21-2.

5 The partial human STLK7 cDNA (SEQ ID NO:100) is 311 bp long and consists of a 309 bp ORF. Since the coding region is open throughout the 5' and 3' extent of this sequence, this appears to be a partial cDNA clone lacking the N-terminal start methionine and C-terminal stop codon.

10 STLK7 shares 80% sequence identity to human SPAK (AF099989) over a 167 bp region and 50% nucleotide sequence identity to SLTK7 (SEQ ID NO. 101) over 391 nucleotides.

#### cDNA Cloning and Characterization of ZC1

15 The human ZC1 cDNA sequence is composed of two overlapping PCR clones, 3R25-24-2 and R65-12-2.

A human ZC1 clone, 125-33-5, was first identified from a PCR screen with degenerate oligos, TRK1 and TRK4, applied to ssDNA generated from human small airway epithelial cells (Clontech). Sequence analysis of the 503 bp insert  
20 identified a 501 bp ORF (167 amino acids) with the potential to encode a novel human STK related to the *C. elegans* ZC504.4 gene product.

PCR clone 3R25-24-2 was isolated from human SNB19 glioblastoma ssDNA using primers 5'-ATGGCGAACGACTCTCCCGCGAA  
25 and 5'-ACACCAAAATCAACAAGTTTCACCTC derived from the N-terminus of a murine orthologue of ZC1 (NIK, GB:U88984) and the original human ZC1 clone 125-33-5, respectively. 3R25-24-2 contains a 527 bp insert and an ORF of 519 bp (173 amino acids).

30 PCR clone R65-12-2 was isolated as follows: A Smith-Waterman search of the EST database with the *C. elegans* ZC504.4 gene (GB:Z50029) as a query identified a human EST (W81656) whose ORF is related to the *C. elegans* gene and



terminates in an identical residue (Trp). A primer was designed 3' to this stop codon (5'-AGTTACAAGGAATTCCAAGTTCT) and used in a PCR reaction with a primer derived from the original human ZC1 clone 125-33-5 (5'-

5 ATGAAGAGGAAGAAATCAAACCTG) using ssDNA from human SNB19 glioblastoma as a template. PCR clone R65-12-2 was identified and was found to contain a 3611 bp insert with a 3534 bp ORF encoding the C-terminal portion of human ZC1 (1178 amino acids).

10 The full-length human ZC1 cDNA (SEQ ID NO. 9) is 3798 bp long. Clone 3R25-24-2 spans positions 1-527, and clone R65-12-2 spans positions 188-3798. The overlap between these two clones exhibits 100% sequence identity. The human ZC1 contains a 3717 bp ORF (17-3723) flanked by a 6 bp 5' 15 UTR and a 75 bp (3724-3798) 3' UTR. No polyadenylation signal (AATAAA) or polyadenylated region are present in the 3'UTR. The sequence flanking the first ATG conforms to the Kozak consensus for an initiating methionine, and is believed to be the translational start site for human ZC1.

20 Multiple EST fragments (W81656) match the 3' end of the human ZC1 gene, but at the time of filing, the inventors believe that none exist in GenBank or the EST database that match its 5' end.

## 25 cDNA Cloning and Characterization of ZC2

The human ZC2 cDNA sequence is composed of four overlapping PCR clones, G75-31-17, R65-24-6, 2R28-8-1, and R99-6-10.

30 A human ZC2 clone, G75-31-17, was first identified from a PCR screen with degenerate oligos, ROS1 (5'-GCNTTYGGNGARGTNTAYGARGG) and CCK4b (5'-GCTGGATCCYTCNGGNSWCATCCA), applied to ssDNA generated from the human HLT383 primary non-small cell lung cancer tissue.

Sequence analysis of the 492 bp insert identified a 492 ORF (164 amino acids) with the potential to encode a novel human STK related to the *C. elegans* ZC504.4 gene product.

5 PCR clone R99-6-10 was isolated as follows: A Smith-Waterman search of the EST database with *C. elegans* ZC504.4 gene (GB:Z50029) as a query identified two overlapping human EST fragments (AA115844 and R51245) whose ORFs were related to the *C. elegans* gene and terminate in an identical residue (Trp). A primer was designed 3' to the stop codon found in  
10 R51245 (5'-AGATGGACTGTACTGGGAGG) and used in a PCR reaction with a primer derived from AA115844 (5'-ACTTTGTGCAGCTCTGTGGG) using human fetal brain ssDNA as a template. PCR clone R99-6-10 was identified and was found to contain a 1095 bp insert with a 930 bp ORF encoding the  
15 C-terminal portion of human ZC2 (310 amino acids).

PCR clone R65-24-6 was isolated from human HT29 colon cancer cell line ssDNA using primers 5'-AAGGTTATGGATGTCACAGGG and 5'-AGATGGACTGTACTGGGAGG derived from G75-31-17 and R51245, respectively. The 3' primer used  
20 in this PCR reaction misprimed between positions 1634-1653 of this gene leading to the formation of a truncated product. R65-24-6 contains a 1593 bp insert and an ORF of 1593 bp (531 amino acids).

PCR clone 2R28-8-1 was isolated from human colon cancer  
25 cell line HT29 ssDNA using primers 5'-CTCACAAGGTTGCCAACAGG and 5'-AGTCCCCACCAGAAGGTTTAC derived from R65-24-6 and R99-6-10, respectively. 2R28-8-1 contains a 1538 bp insert and an ORF of 1536 bp (512 amino acids).

The partial human ZC2 cDNA (SEQ ID NO. 10) is 4055 bp  
30 long. Clone G75-31-17 spans positions 1-492, clone R65-24-6 spans positions 58-1650, clone 2R28-8-1 spans positions 1466-3003 and clone R99-6-10 spans positions 2961-4055. The overlapping regions between these clones exhibit 100%

sequence identity except for a single guanine (G75-31-17) to adenosine (R65-24-6) mismatch at position 280 resulting in a Glu to Lys change. Based on the presence of an acidic residue in this position in human ZC1 and ZC3 and *C. elegans* ZC504.4, the sequence encoding the Glu is probably correct.

The human ZC2 gene contains a 3891 bp ORF (1-3891) flanked by 164 bp (3892-4055) 3' UTR. No polyadenylation signal (AATAAA) or polyadenylated region is present in the 3'UTR.

Multiple EST fragments (R51245) match the 3' end of the human ZC2 gene, but at the time of filing, the inventors believe that none exist in GenBank or the EST database that match its 5' end.

#### cDNA Cloning and Characterization of ZC3

The human ZC3 cDNA sequence is composed of four overlapping PCR clones, G75-30-30, 3R33-5-3, 3R19-17-6, and R99-43-11.

A human ZC3 clone, G75-30-30, was first identified from a PCR screen with degenerate oligos, ROS1 and CCK4b, applied to ssDNA generated from a human HLT370 primary non-small cell lung cancer tissue. Sequence analysis of the 492 bp insert identified a 492 ORF (164 amino acids) with the potential to encode a novel human STK related to the *C. elegans* ZC504.4 gene product.

PCR clone R99-43-11 was isolated as follows: A Smith-Waterman search of the EST database with the *C. elegans* ZC504.4 gene (GB:Z50029) as a query identified a human EST (R54563) whose ORF is related to the *C. elegans* gene and terminates in an identical residue (Trp). A primer was designed 3' to the stop codon found in R54563 (5'-TCAGGGGTCAGAGGTCACG) and used in a PCR reaction with a primer derived from the 5' end of R54563 (5'-CCCAAACCCTACCACAAATTC) using ssDNA from human fetal brain

as a template. PCR clone R99-43-11 was identified and was found to contain a 719 bp insert with a 564 bp ORF encoding the C-terminal portion of human ZC3 (188 amino acids).

5 PCR clone 3R19-17-6 was isolated from human A549 lung cancer cell line ssCDNA using primers 5'-CCCCCGGGAAACGATGACCA and 5'-AGCCGCTGCCCCCTCCTACTGT derived from G75-30-30 and R99-43-11, respectively. The 3' primer used in this PCR reaction misprimed leading to the formation of a truncated product. 3R19-17-6 contains a 1172 bp insert and an ORF of 1170 bp (390 amino acids).

10 PCR clone 3R33-5-3 was isolated from human A549 lung cancer cell line ssCDNA using primers 5'-ACCGCAACATCGCCACCTACTAC and 5'-CTCGACGTCGTGGACCACC derived from G75-30-30 and 3R19-17-6, respectively. 3R33-5-3 contains a 2465 bp insert and an ORF of 2463 bp (821 amino acids).

15 The full-length human ZC3 cDNA (SEQ ID NO. 11) is 4133 bp long. Clone G75-30-30 spans positions 1-483, clone 3R33-5-3 spans positions 134-2598, clone 3R19-17-6 spans positions 2356-3512 and clone R99-43-11 spans positions 3415-4133. The overlaps between these clones exhibit 100% sequence identity. The human ZC3 gene contains a 3978 bp ORF (1-3978) flanked by a 152 bp 3' UTR (3979-4133). No polyadenylation signal (AATAAA) or polyadenylated region is present in the 3'UTR.

20 Multiple EST fragments (R54563) match the 3' end of the human ZC3 gene, but at the time of filing, the inventors believe that none exist in GenBank or the EST database that match its 5' end.

cDNA Cloning and Characterization of ZC4

The human ZC4 cDNA sequence, represented by PCR fragment 3R25-27-1, was first identified in the human genomic cosmid 82J11 (GB:Z833850) containing exon sequences that displayed strong homology to the ZC504.4 *C. elegans* gene.

PCR clone 3R25-27-1 was isolated from human fetal liver ssDNA and primers 5'-CAATGTTAACCCACTCTATGTCTC and 5'-AGTTTGCCGATGTTTTCTTTTC derived from a potential ORF (positions 25729-25852) from the 82J11 cosmid and from an EST (R98571) encoding the C-terminus of the human ZC4 gene, respectively.

The partial human ZC4 cDNA (SEQ ID NO.12) is 1459 bp long and consists of a 1047 bp ORF (2-1048) flanked by a 411 bp (1049-1459) 3'UTR region. No polyadenylation signal (AATAAA) or polyadenylated region is present in the 3'UTR.

The N-terminal coding sequence for ZC4\_h was extended by building a contiguous DNA sequence of 233,137 bp containing Z83850 and four other sequences: cU84B10 and cU230B10 (from the Sanger Human Genome Sequencing Project, <http://www.sanger.ac.uk/HGP/>) and Z97356 and Z69734 (available from the National Institute for Biotechnology Information, <http://www.ncbi.nlm.nih.gov/Entrez/nucleotide.html>). The position of each sequence in the contig is represented in the table below.

Accession	Length	Start	End
cU84B10	43273	0	43273
Z97356	21848	43171	65018
Z69734	37077	63073	100149
cU230B10	11841	88416	100256
Z83850	132981	100156	233137

Sequences in ZC4 genomic contig.

The 233,137 bp contig was analyzed for exons using the programs FGENES 1.5 and FGENESH, human gene structure prediction software available from The Sanger Centre (<http://genomic.sanger.ac.uk/qf/qf.shtml>).

- 5 The resulting human ZC4 coding sequence (SEQ ID NO:104) is 3,681 bp long (excluding the stop codon) and encodes for a STE20 kinase of 1227 amino acids.

#### cDNA Cloning and Characterization of KHS2

- 10 The human KHS2 cDNA sequence is composed of four overlapping clones, 3R25-51-2, 3R16-34-2, 3R16-31-2, and T79916.

- A human KHS2 clone, AA250855, was first identified using a Smith-Waterman search of the EST database with KHS1 (GB:U77129) as a query. Sequence analysis of the 1112 bp insert identified a 618 bp ORF (206 amino acids) with the potential to encode a novel STK related to the human KHS1 gene product. Using AA250855 as a query, a second EST (AA446022) was found whose sequence was shown to contain the initiator methionine for human KHS2 based on a comparison with KHS1.

- 20 PCR clone 3R25-51-2 was isolated from human testicular cancer sscDNA using primers 5'-CCGCCATGAACCCCGGCTT and 5'-CGATTGCCAAAGACCGTGTCA derived from AA446022 and AA250855, respectively. 3R25-51-2 contains an 850 bp insert and an ORF of 849 bp (283 amino acids).

- EST clone, T79916, was identified using a Smith-Waterman search of the EST database with the C-terminus of KHS1 (GB:U77129) as a query. Sequence analysis of the 2107 bp insert identified this EST to contain an ORF of 345 bp (115 amino acids disrupted by a single stop codon) encoding the C-terminus of human KHS2, followed by 1762 bp 3'UTR.

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PCR clone 3R16-34-2 was isolated from human testis  
sscDNA using primers 5'-AGAAGTTGCAGCTGTTGAGAGGA and 5'-  
TATGGCCCGTGTAAAGGATTTC derived from AA250885 and T79916,  
respectively. 3R16-34-2 contains an 1516 bp insert and an  
5 ORF of 1128 bp (376 amino acids).

PCR clone 3R16-31-2 was isolated from normal human  
colon sscDNA using primers 5'-GTGCCAGAAGTGTGTGTTGTAA and  
5'-TATGGCCCGTGTAAAGGATTTC derived from EST T79916. 3R16-31-2  
contains a 728 bp insert and an ORF of 669 bp (223 amino  
10 acids). This clone lacked the stop codon present within EST  
T79916 (position 2662 in the KHS2 sequence).

The full-length human KHS2 cDNA (SEQ ID NO.17) is 4023  
bp long. Clone 3R25-51-2 spans positions 1-855, clone  
AA250885 spans positions 336-923, clone 3R16-34-2 spans  
15 positions 545-2061, and clone T79916 spans positions 1917-  
4023. The overlapping regions between these clones exhibit  
100% sequence identity, except for 4 nucleotide differences,  
two of which are silent, a third corrects the internal stop  
codon at position 2662, and the fourth at position 247 (T to  
20 C change) results in a Pro to Leu change. The human KHS2  
cDNA contains a 2682 bp ORF (6-2687) flanked by a 5 bp (1-5)  
5'UTR and a 1336 bp (2688-4023) 3' UTR. A potential  
polyadenylation signal (AATAAA) is found at positions 4008-  
4013. No polyadenylated region is present in the 3'UTR. The  
25 sequence flanking the first ATG is in a poor context for  
translational initiation, however, a 134 bp 5'UTR sequence  
from EST AA446022 did not reveal any additional ATG's and  
displayed two in-frame stop codons 5' to the putative start  
ATG for human KHS2.

30 Multiple EST fragments match the 5' end (AA446022) as  
well as the 3' end (R37625) of the human KHS2 gene.

cDNA Cloning and Characterization of SULU1

The human SULU1 cDNA sequence is composed of three overlapping clones, N40091, 2R90-1-1 and R90907.

5 A human SULU1 clone, N40091, was first identified using a Smith-Waterman search of the EST database with the *C. elegans* SULU gene (GB: U32275) as a query. Sequence analysis of the 1321 bp insert identified a 906 bp ORF (302 amino acids) with the potential to encode a novel human STK related to the *C. elegans* SULU gene product.

10 EST clone R90907 was first identified using a Smith-Waterman search of the EST database with the 3' end of the *C. elegans* SULU gene (GB: U32275) as a query. Sequence analysis of the 1647 bp insert identified a 578 bp ORF (192 amino acids) with the potential to encode the C-terminus of  
15 the human SULU1 gene product.

PCR clone 2R90-1-1 was isolated from human HT29 colon cancer cell ssDNA using primers 5'- TATTGAATTGGCGGAACGGAAG and 5'- TTGTTTGTGCTCATTCTTTGGAG derived from N40091 and R90907, respectively. 2R90-1-1 contains a 1625 bp insert  
20 and an ORF of 1623 bp (541 amino acids).

The full-length human SULU1 cDNA (SEQ ID NO.19) is 4177 bp long. Clone N40091 spans positions 1-1321, clone 2R90-1-1 spans positions 1048-2671, and clone R90907 spans positions 2531-4177. The overlapping regions between these clones  
25 exhibit 100% sequence identity. The human SULU1 cDNA contains a 2694 bp ORF (415-3108) flanked by a 414 bp (1-414) 5'UTR and a 1069 bp (3109-4177) 3' UTR followed by a 19 nucleotide polyadenylated region. A potential polyadenylation signal (AATAAA) is found at positions 4164-  
30 4169. The sequence flanking the first ATG conforms to the Kozak consensus for an initiating methionine, and is believed to be the translational start site for human SULU1.



Multiple EST fragments match the 5' end (N27153) as well as the 3' end (R90908) of the human SULU1 gene.

cDNA Cloning and Characterization of Murine SULU3

5 The murine SULU3 cDNA sequence is represented by PCR fragment 2R92-1-6.

A murine SULU3 clone, G83-4-5, was first identified from a PCR screen with degenerate oligos, CCK4c and CCK4b, applied to ssDNA generated from murine day-12 embryos. Sequence analysis of the 473 bp insert identified a 471 ORF (157 amino acids) with the potential to encode a novel human STK related to the *C. elegans* SULU gene (GB: U32275) product. The antisense strand of G83-4-5 is identical at the nucleic acid level to the 5'UTR of the murine ets1 protooncogenic transcription factor (GB:X53953). This homology is likely the result of a cloning artifact attached to the 5'-end of the database entry for murine ets1.

PCR clone 3R19-17-6 was isolated from human A549 cell ssDNA using primers 5'-CCCCCGGAAACGATGACCA and 5'-AGCCGCTGCCCCCTCCTCTACTGT derived from G75-30-30 and R99-43-11, respectively. The 3' primer used in this PCR reaction misprimed leading to the formation of a truncated product. 3R19-17-6 contains a 1172 bp insert and an ORF of 1170 bp (390 amino acids).

25 PCR clone 2R92-1-6 was isolated from murine d8 embryo ssDNA using primers 5'-ACCGCAACATCGCCACCTACTAC and 5'-GATTGCTTTGTGCTCATTCTTTGG derived from the 5' UTR of the ets1 gene and the human EST AA234623, respectively. The latter (shown herein) encodes the C-terminus of human SULU3. 2R92-1-6 contains a 2249 bp insert and an ORF of 2244 bp (748 amino acids).

The partial murine SULU3 cDNA (SEQ ID NO.21) is 2249 bp long and consists of a 2244 bp ORF (6-2249) flanked by a 5

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bp (1-5) 5'UTR. The sequence flanking the first ATG conforms to the Kozak consensus for an initiating methionine, and is believed to be the translational start site for murine SULU3.

- 5 One EST fragment (AA446022) matches the 3' end of the partial murine SULU3 gene, but at the time of filing, the inventors believe that none exist in GenBank or the EST database that match its 5' end.

10 cDNA Cloning and Characterization of Human SULU3

The human SULU3 cDNA sequence is composed of two overlapping clones, 2R90-22-1 and AA234623.

- 15 A human SULU3 clone, AA234623, was first identified using a Smith-Waterman search of the EST database with the *C. elegans* SULU gene (GB: U32275) as a query. Sequence analysis of the 2652 bp insert identified a 1185 bp ORF (395 amino acids) with the potential to encode the C-terminus of a novel human STK related to the *C. elegans* SULU gene product.

- 20 PCR clone 2R90-22-1 was isolated from human SKMel128 melanoma cell line ssDNA using primers 5'-TATTGAATTGGCGGAACGGAAG and 5'- TTGTTCTAAGAGTGCCCTCCG derived from the murine SULU3 2R92-1-6 clone and from AA234623, respectively. 2R92-1-6 contains a 1897 bp insert and an ORF of 1896 bp (632 amino acids).

- 25 The partial human SULU3 cDNA (SEQ ID NO.20) is 3824 bp long. Clone 2R90-22-1 spans positions 1-1897 and clone AA234623 spans positions 1173. The overlapping region between these clones exhibits 100% sequence identity. The human SULU3 cDNA contains a 2358 bp ORF (2-2359) flanked by a 1465 bp (2360-3824) 3'UTR followed by a 19 nucleotide polydenylated region. A potential polyadenylation signal (AATAAA) is found at positions 2602-2607. Since the coding
- 30

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region is open throughout the 5' extent of this sequence, this is apparently a partial cDNA clone lacking the N-terminal start methionine.

5 Multiple EST fragments (R02283) match the 3' end of the human SULU3 gene, but at the time of filing, the inventors believe that none exist in GenBank or the EST database that match its 5' end.

cDNA Cloning and Characterization of GEK2

10 The human GEK2 cDNA sequence is composed of three overlapping clones, AA459448, 3R25-48-1 and GEK2\_h#3.

A human GEK2 clone, AA459448, was first identified using a Smith-Waterman search of the EST database with the human SLK gene (GB: AB002804) as a query. Sequence analysis  
15 of the 1286 bp insert identified a 1227 bp ORF (409 amino acids) with the potential to encode the N-terminus of a novel human STK related to the human SLK gene product. An additional Smith-Waterman search using the C-terminus of the SLK gene as a query yielded three additional EST's,  
20 AA323687, AA380492 and AA168869, that encode the C-terminal region of human GEK2.

PCR clone 2R98-41-17 was isolated from human testis  
sscDNA using primers 5'- AAGACCATGCCGTGCGCCG and 5'-  
ATTCCTTCAGGTTCTGGTTATGG derived from AA323687 and from  
25 AA380492, respectively. 2R98-41-17 contains a 851 bp insert and an ORF of 849 bp (283 amino acids).

PCR clone GEK2\_h#3 was isolated from human sscDNA made from the H23 tumor cell line using primers 5'-  
GCAGCAAGTGGAGAAGATGG and 5'- GGAAGCATCCCCAGAGCTGTAG derived  
30 from the sequence of clone 3R25-48-1 and from the 3' end of murine LOK (GB:D89728), respectively. GEK2\_h#3 contains a 1042bp insert and an ORF of 1041 bp (347 amino acids).

The full-length human GEK2 cDNA (SEQ ID NO:106) is 2962 bp long. Clone AA459448 spans positions 1-1286, clone 3R25-48-1 spans positions 1100-2449 and clone GEK2\_h#3 spans positions 1920-2962. The overlapping regions between these clones exhibit 100% sequence identity.

The human GEK2 cDNA contains a 2904 bp ORF (59-2962) flanked by a 58 bp (1-58) 5'UTR. The sequence flanking the first ATG conforms to the Kozak consensus for an initiating methionine, and is believed to be the translational start site for human GEK2.

Multiple EST fragments (AA465671) match the 5' end of the sequence, but only one (AA380492) matches the 3' end of the human GEK2 gene.

#### 15 cDNA Cloning and Characterization of PAK4

The human PAK4 cDNA sequence is represented by clone SNB2#1.

A human PAK4 clone, R88460, was first identified using a Smith-Waterman search of the EST database with the human PAK gene (GB: U24152) as a query. Sequence analysis of the 2332 bp insert identified a 930 bp ORF (310 amino acids) with the potential to encode the C-terminus of a novel human STK related to the human PAK gene product.

cDNA clone SNB2#1 was isolated from human glioblastoma cell line SNB75 cDNA library using a probe derived from R88460. SNB2#1 contains a 3604 bp insert and an ORF of 2043 bp (681 amino acids).

The full-length human PAK4 cDNA (SEQ ID NO.27) is 3604 bp long and consists of a 2043 bp ORF (143-2185) flanked by a 142 bp (1-142) 5'UTR and a 1419 3' UTR followed by a 22 nucleotide polydenylated region. A potential polyadenylation signal (AATTAAA) is found at positions 3582-3588. The sequence flanking the first ATG conforms to the

Kozak consensus for an initiating methionine, and is believed to be the translational start site for human PAK4.

5 The 3' UTR of the PAK4 gene contains a GT dinucleotide repeat prone to undergo expansion based on the number of repeats found in clones SNB#1 and R88460, 32 and 23, respectively. Several neurologic disorders have been correlated with the expansion of di- or tri-nucleotide repeats similar to those found in the PAK4 sequence, suggesting PAK 4 may also be a disease target and that this  
10 repeat in its 3'UTR may serve as a diagnostic marker.

Multiple EST fragments (AA535791) match the 3' end of the human PAK4 gene, but at the time of filing, the inventors believe that none exist in GenBank or the EST database that match its 5' end.

15

#### cdNA Cloning and Characterization of PAK5

The full-length human PAK5 cDNA sequence is composed of two overlapping clones, H450#1-1 and SNB8#5.

20 A human PAK5 clone, R18825, was first identified using a Smith-Waterman search of the EST database with the human PAK4 gene as a query. Sequence analysis of the 1248 bp insert identified a 420 bp ORF (140 amino acids) with the potential to encode the C-terminus of a novel human STK related to the human PAK4 gene product.

25 cdNA clone SNB8#5 was isolated from human SNB75 cDNA library using a probe derived from R18825. SNB2#1 contains a 2028 bp insert and an ORF of 1194 bp (398 amino acids).

The partial human PAK5 cDNA (SEQ ID NO.28) is 2028 bp long and consists of a 1194 bp ORF (2-1195) flanked by an  
30 833 bp (1196-2028) 3'UTR followed by a 22 nucleotide polydenylated region. A potential polyadenylation signal (AATTAAA) is found at positions 2004-2010. Since the coding region is open throughout the 5' extent of this sequence,

this is apparently a partial cDNA clone lacking the N-terminal start methionine.

Clone H460#1-1 was isolated from a human lung H460 cDNA library using a probe derived from the partial SNB2#1 cDNA clone described above. Sequence analysis of the 2526 bp insert identified a 1773 bp ORF (592 amino acids) with the potential to encode a full-length PAK5.

The human PAK5 cDNA (SEQ ID NO:102) is 2,806 bp long and consists of a 1,773 bp ORF flanked by a 201 bp 5' UTR and a 833 bp 3' UTR. The sequence flanking the first ATG conforms to the Kozak consensus (Kozak, M., Nucleic Acids Res. 15, 8125-8148 (1987)) for an initiating methionine, and is believed to be the translational start site for PAK5.

PAK5 shares 99% sequence identity over 2795 bp to a recent database entry, AF005046. These sequences are presumed to be from the same gene, with minor polymorphic variations.

#### EXAMPLE 2: Expression Analysis of Mammalian STE20-related

##### Protein Kinases

##### Materials and Methods

##### Northern blot analysis

Northern blots were prepared by running 10 g total RNA isolated from 60 human tumor cell lines (HOP-92, EKVX, NCI-H23, NCI-H226, NCI-H322M, NCI-H460, NCI-H522, A549, HOP-62, OVCAR-3, OVCAR-4, OVCAR-5, OVCAR-8, IGROV1, SK-OV-3, SNB-19, SNB-75, U251, SF-268, SF-295, SF-539, CCRF-CEM, K-562, MOLT-4, HL-60, RPMI 8226, SR, DU-145, PC-3, HT-29, HCC-2998, HCT-116, SW620, Colo 205, HTC15, KM-12, UO-31, SN12C, A498, CaKi1, RXF-393, ACHN, 786-0, TK-10, LOX IMVI, Malme-3M, SK-MEL-2, SK-MEL-5, SK-MEL-28, UACC-62, UACC-257, M14, MCF-7, MCF-7/ADR RES, Hs578T, MDA-MB-231, MDA-MB-435, MDA-N, BT-549, T47D), from 22 human adult tissues (thymus, lung,

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duodenum, colon, testis, brain, cerebellum, cortex, salivary gland, liver, pancreas, kidney, spleen, stomach, uterus, prostate, skeletal muscle, placenta, mammary gland, bladder, lymph node, adipose tissue), and 2 human fetal normal tissues (fetal liver, fetal brain ), on a denaturing formaldehyde 1.2% agarose gel and transferring to nylon membranes.

Filters were hybridized with random primed [ $\alpha^{32}\text{P}$ ]dCTP-labeled probes synthesized from the inserts of several of the STE20-related kinase genes. Hybridization was performed at 42 °C overnight in 6X SSC, 0.1% SDS, 1X Denhardt's solution, 100  $\mu\text{g/mL}$  denatured herring sperm DNA with 1-2 x  $10^6$  cpm/mL of  $^{32}\text{P}$ -labeled DNA probes. The filters were washed in 0.1X SSC/0.1% SDS, 65 °C, and exposed on a Molecular Dynamics phosphorimager.

#### Quantitative PCR analysis

RNA was isolated from a variety of normal human tissues and cell lines. Single stranded cDNA was synthesized from 10  $\mu\text{g}$  of each RNA as described above using the Superscript Preamplification System (GibcoBRL). These single strand templates were then used in a 25 cycle PCR reaction with primers specific to each clone. Reaction products were electrophoresed on 2% agarose gels, stained with ethidium bromide and photographed on a UV light box. The relative intensity of the STK-specific bands were estimated for each sample.

#### DNA Array Based Expression Analysis

Plasmid DNA array blots were prepared by loading 0.5  $\mu\text{g}$  denatured plasmid for each STE20-related kinase on a nylon membrane. The [ $\alpha^{32}\text{P}$ ]dCTP labeled single stranded DNA probes were synthesized from the total RNA isolated from several

human immune tissue sources or tumor cells (thymus, dendrocytes, mast cells, monocytes, B cells (primary, Jurkat, RPMI8226, SR), T cells (CD8/CD4+, TH1, TH2, CEM, MOLT4), K562 (megakaryocytes). Hybridization was performed at 42 °C for 16 hours in 6X SSC, 0.1% SDS, 1X Denhardt's solution, 100 µg/mL denatured herring sperm DNA with 10<sup>6</sup> cpm/mL of [ $\alpha^{32}$ P]dCTP labeled single stranded probe. The filters were washed in 0.1X SSC/0.1% SDS, 65 °C, and exposed for quantitative analysis on a Molecular Dynamics phosphorimager.

### RESULTS

#### Distribution of STE20-Related Gene Transcripts in Normal Tissues and Tumor Cell Lines

ZC1, ZC2, and ZC3 RNA expression was analyzed by quantitative PCR from multiple human normal tissues, cultured primary epithelial and endothelial cells, and tumor cell lines. The results are summarized in Tables 1 and 2, with relative expression values ranging from 0 (undetectable) to 23 (very strong). An "x" refers to sample not tested. ZC1, ZC2, and ZC3 were all expressed at very low levels in most normal human tissues, however ZC1 and ZC2 were more abundant in cultured epithelial cells and ZC3 in normal kidney and breast tissue.

Expression of these 3 genes was also examined in a panel of human tumor cell lines representing a diverse sampling of tumor types (Table 2). ZC1 and ZC2 showed strong expression in cell lines from most melanomas and renal tumors and from some non-small cell lung cancers and colon tumors. ZC3 expression was consistently lower in the tumor cell lines except for high expression in most breast cancers and leukemias. The robust overexpression ZC1, ZC2,



and ZC3 in tumor cells versus normal tissues may provide an attractive target for oncology drug development.

Expression of all the novel STE20-related kinases was examined in a panel of human immune tissues/cells by hybridization to a DNA array blot containing plasmids encoding each of these genes. STLK2 was broadly expressed in all 14 immune samples, whereas STLK4 and PAK4 were highly expressed in a subset of 6-7 of the samples (Table 3). Several other kinases (SULU3, ZC4, KHS2) had more restricted expression, while others were expressed in only a single immune source (STLK3, thymus; ZC1, dendrocytes; ZC3, monocytes; PAK5, mast cells and MOLT4), and several more were absent from all the immune sources assayed (GEK2, SULU1, ZC2, STLK5). These expression patterns were quite distinct among members of the same subfamily (i.e., ZC1, ZC2, ZC3 and ZC4, or PAK1, PAK2, PAK3, PAK4, PAK5). This analysis suggests that some of these kinases may be candidate targets for various immune disorders, and that some, which are more broadly expressed, may mediate functions vital to the basic biology of most proliferating cells.

TABLE 1

ZC1, ZC2 and ZC3 Expression  
in Normal Human Tissues and Cells

Sample		ZC1	ZC2	ZC3
NORMAL				
Brain	Tiss	2.8	0.6	0.9
Duod	Tiss	3.8	1.5	0.3
Heart	Tiss	1.2	0.3	0.0
Kidney	Tiss	0.7	0.0	7.0
Lung	Tiss	1.6	0.2	0.0
Pancreas	Tiss	2.0	0.4	2.5

Placenta	Tiss	1.4	0.0	0.0
Sal gl.	Tiss	3.0	0.3	3.2
Sk mus.	Tiss	2.3	0.1	0.1
Spleen	Tiss	0.4	0.0	x
Stomach	Tiss	0.8	0.0	0.0
Thymus	Tiss	3.5	0.4	1.5
Cereb	Tiss	2.8	1.1	4.4
Liver	Tiss	1.8	0.0	0.4
Uterus	Tiss	1.6	0.0	1.4
Prostate	Tiss	1.4	0.0	1.6
Testis	Tiss	x	x	5.8
f Brain	Tiss	x	x	3.1
Mam gl	Tiss	x	x	7.2
HCAEC	ENDO	1.0	0.0	0.0
HMVEC-d	ENDO	0.7	0.0	0.4
HMVEC-L	ENDO	2.2	1.6	1.8
HPAEC	ENDO	9.3	5.3	6.4
HMEC	EPI	4.1	2.3	1.9
RPTEC	EPI	3.6	2.2	0.2
HRCE	EPI	5.3	3.5	1.3
HSAE	EPI	0.9	3.3	4.8

TABLE 2

ZC1, ZC2 and ZC3 Expression in Tumor Cell lLnes

Sample	Origin	ZC1	ZC2	ZC3
HOP-92	Lung	9.3	7.2	3.3
EKVX	Lung	10.7	3.7	3.5
NCI-H23	Lung	5.8	6.3	4.1
NCI-H226	Lung	6.5	6.8	3.3

Sample	Origin	ZC1	ZC2	ZC3
HCC-2998	Colon	2.4	3.8	3.0
HCT 116	Colon	2.2	2.1	5.4
SW-620	Colon	7.8	12.1	3.1
COLO 205	Colon	9.1	16.2	3.0

NCI-H322M	Lung	3.5	5.8	4.9
NCI-H460	Lung	4.5	3.7	2.9
NCI-H522	Lung	4.7	3.3	4.6
A549/ATCC	Lung	3.8	3.6	4.1
HOP-62	Lung	4.3	3.8	4.2
OVCAR-3	Ovary	2.9	3.1	1.5
OVCAR-4	Ovary	3.3	1.0	3.8
OVCAR-5	Ovary	2.6	3.6	2.2
OVCAR-8	Ovary	3.6	2.0	4.7
IGROV1	Ovary	3.8	1.7	3.2
SK-OV-3	Ovary	4.9	0.0	3.5
SNB-19	CNS	5.1	5.4	4.2
SNB-75	CNS	2.5	0.9	0.7
U251	CNS	1.5	1.2	0.6
SF-268	CNS	5.8	2.7	3.0
SF-295	CNS	6.4	1.1	3.2
SF-539	CNS	5.1	2.9	4.3
CCRF-CEM	Leuk	3.4	2.7	3.1
K-562	Leuk	4.1	6.3	4.3
MOLT-4	Leuk	7.1	3.4	4.2
HL-60	Leuk	x	x	0.4
RPMI 8226	Leuk	0.5	0.2	1.4
SR	Leuk	3.5	7.2	5.4
DU-145	Pro	x	x	3.4
PC-3	Pro	x	x	3.4
HT-29	Colon	2.4	5.9	6.6

HCT-15	Colon	13.8	4.9	2.5
KM-12	Colon	7.0	13.2	3.1
UO-31	Colon	10.4	10.6	0.9
SN12C	Renal	8.1	3.4	2.8
A498	Renal	6.2	3.1	2.9
Caki-1	Renal	9.2	14.4	2.3
RXF 393	Renal	10.6	4.8	2.8
ACHN	Renal	9.3	6.0	3.9
786-0	Renal	8.8	15.6	5.6
TK-10	Renal	20.9	21.2	5.0
LOX IMVI	Mel	2.3	2.4	3.3
Malme-3M	Mel	x	x	2.2
SK-MEL-2	Mel	15.7	14.1	2.9
SK-MEL-5	Mel	7.9	7.0	0.0
SK-MEL-28	Mel	16.5	23.1	0.0
UACC-62	Mel	12.1	18.3	5.3
UACC-257	Mel	10.8	9.4	6.2
M14	Mel	4.4	0.9	7.9
MCF7	Breast	4.8	1.3	7.7
MCF-7/ADR	Breast	8.8	3.4	7.7
Hs 578T	Breast	6.9	2.6	5.7
MDA-MB-231	Breast	5.7	1.9	6.4
MDA-MB-435	Breast	4.8	6.7	9.1
MDA-N	Breast	7.3	6.3	9.1
BT-549	Breast	3.6	1.9	8.0
T-47D	Breast	0.4	12.3	9.3

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Table 3: STE20-related kinase expression in a human immune panel

KINASE	thymus	Dendro-cytes	Mast cells	Mono-cytes	B cells	CD8+ CD4+	TH1	TH2
GEK2	350	350	350	350	350	350	350	350
SULU1	350	350	350	350	350	350	350	350
SULU3	350	350	350	350	12149	350	5115	350
STLK2	117770	13771	27620	92036	18305	39109	5408	3564
STLK3	8624	350	350	350	350	350	350	350
STLK4	8524	350	350	350	350	8685	5642	350
STLK5	xxx	xxx	xxx	xxx	350	350	350	xxx
ZC1	350	3377	350	350	350	350	350	350
ZC2	350	350	350	350	350	350	350	350
ZC3	350	350	350	20156	350	350	350	350
ZC4	xxx	xxx	xxx	xxx	350	350	350	xxx
KHS2	8766	2508	350	56575	350	350	350	350
PAK4	32658	7684	3729	100948	350	350	350	1604
PAK5	350	350	4905	350	350	350	350	350

KINASE	CEM (T cell)	MOLT4 (T cell)	JURKAT (B cell)	RPMI8226 (B cell)	SR (B cell)	K562 (MO)
GEK2	350	350	350	350	350	350
SULU1	350	350	350	350	350	350
SULU3	350	350	350	350	350	350
STLK2	47236	53262	47605	22560	65936	30390
STLK3	350	350	350	350	350	350
STLK4	3648	350	26772	1570	350	350
STLK5	350	350	350	xxx	350	350
ZC1	350	350	350	350	350	350

ZC2	350	350	350	350	350	350
ZC3	350	350	350	350	350	350
ZC4	1094	7813	14945	xxx	350	6385
KHS2	350	350	350	350	350	350
PAK4	350	10246	350	3229	350	350
PAK5	350	12672	350	350	350	350

## Transcript size from Northern data

Kinase	(kb)
STLK2	3.8
STLK4	5.0
ZC1	6.9/4.7
ZC2	6.0/8.0
ZC4	5
KHS2	4.4
SULU1	4.5
SULU3	10.0
GEK2	5.5
PAK4	4.8
PAK5	3.5

STLK2 is widely expressed; the highest expression levels were found in placenta, spleen and PBL.

STLK4 is also widely expressed in normal tissues including heart, brain, placenta, lung, liver, skeletal muscle, kidney, pancreas, spleen, thymus, prostate, testis, ovary, small intestine, colon, and peripheral blood lymphocytes. STLK4 was also detected in Jurkat T cells.

ZC1 is highly overexpressed in the following human cancer cell lines: HOP-92, EKVX, NCI-H23, NCI-H226, NCI-H322M, NCI-H522, A549, HOP-62 (lung); OVCAR-3, OVCAR-4, OVCAR-5 (ovary); SNB-19, U251, SF-268, SF-295, SF-539 (CNS); K-562, RPMI-8226 (leukemia); DU-145, PC-3 (prostate); HT-29, HCC-2998, HCT-116, SW620, COLO-205, HCT-15, KM-12 (colon); UO-31, CAKi-1, RXF-393, 786-0, TK-10 (renal); LOXIMVI, Malme-3M, SK-MEL-2, SK-MEL-28, UACC-62, UACC-257, M14

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(melanoma); and MCF-7, MCF-7/ADR, HIS 578T, MDA-MB-231, MDA-MB-431, MDA-N, BT-549, T-47D (breast).

ZC2 is expressed in brain and testis. It is highly overexpressed in the following human cancer cell lines: TK-10 (renal); SK-MEL-28, UACC-62 (melanoma); T47D (breast).

Moderate expression in HOP92 (lung); OVCAR4, IGROV1 (ovary); DNB75, U251 (brain); K-562 (leukemia); and COLO205 (colon).

SULU1 is overexpressed in the following human cancer cell lines: HOP-92, EKVX, NCI-H23, NCI-H226, NCI-H322M, NCI-H522, A549, HOP-62 (lung); OVCAR-3, OVCAR-4, OVCAR-5, SK-OV-3 (ovary); SNB-19, U251, SF-268, SF-295, SF-539 (CNS); K-562, RPMI-8226 (leukemia); DU-145, PC-3 (prostate); HT-29, HCC-2998, HCT-116, SW620, COLO-205, HCT-15, KM-12 (colon); UO-31, CAKi-1, RXF-393, 786-0, TK-10 (renal); LOX, IMVI, Malme-3M, SK-MEL-2, SK-MEL-28, UACC-62, UACC-257, M14 (melanoma); MCF-7, MCF-7/ADR, HIS 578T, MDA-MB-231, MDA-MB-431, MDA-N, BT-549, T-47D (breast)

SULU3 showed a broad pattern of expression in the normal tissue panel of RNAs.

GEK2 was expressed in spleen, thymus and testis. Expression was high in the cell lines RBL-2H3 and H441.

PAK4 was expressed in the normal tissues: brain, testis and prostate, and in the human cancer cell lines: HNCI-H23 (lung); OVCAR-3 (ovary); SNB-19, U251 (CNS); RPMI-8226 (leukemia); DU-145 (prostate); COLO-205, HCT-15 (colon).

PAK5 showed weak expression levels in the normal tissues: brain, testes, bladder, colon, adrenal medulla, spleen, fetal liver, breast, cerebral cortex, cerebellum, thymus, salivary gland, lung, stomach, duodenum, uterus, prostate, skeletal muscle and placenta. PAK5 was overexpressed in the human cancer cell lines: HOP-92, EKVX, NCI-H23, NCI-H226, NCI-H322M, NCI-H522, A549, HOP-62 (lung);

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OVCAR-3, OVCAR-4, OVCAR-5, SK-OV-3 (ovary); SNB-19, U251, SF-268, SF-295, SF-539 (CNS); K-562, RPMI-8226 (leukemia); DU-145, PC-3 (prostate); HT-29, HCC-2998, HCT-116, SW620, COLO-205, HCT-15, KM-12 (colon); UO-31, CAKi-1, RXF-393, 786-0, TK-10 (renal); LOXIMVI, Malme-3M, SK-MEL-2, SK-MEL-28, UACC-62, UACC-257, M14 (melanoma); MCF-7, MCF-7/ADR, HIS 578T, MDA-MB-231, MDA-MB-431, MDA-N, BT-549, T-47D (breast).

EXAMPLE 3: STE20-related Protein Kinase Gene Expression  
Vector Construction

Materials and Methods

Expression Vector Construction

Several expression constructs were generated for some of the human STE20-related cDNAs including: a) full-length clones in a pCDNA expression vector; b) a GST-fusion construct containing the catalytic domain of the novel STE20-related kinase fused to the C-terminal end of a GST expression cassette; and c) a full-length clone containing a Lys to Ala (K to A) mutation at the predicted ATP binding site within the kinase domain, inserted in the pCDNA vector.

The "K to A" mutants of the STE20-related kinase might function as dominant negative constructs, and will be used to elucidate the function of these novel STKs.

RESULTS

Constructs for ZC1, ZC2, ZC3, SULU1, SULU3, PAK4 and PAK5 have been generated.

Numerous additional constructs have been generated for the various STE20-subfamily kinases, including full length, kinase inactive and tagged versions. In addition, the following three constructs were designed for specific applications based on their unique domain structure:

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Construct 1: SULU1-coiled-coil2

Vector: pGEX-4T

Insert: Coiled-coil2

Sequence: Amino acids 752-898

5 Purpose: phage display

Result: Interacts with GEK2 CC1

Construct 2: SULU3-coiled-coil2

Vector: pGEX4T

10 Insert: coiled-coil 2 domain fused to GST

Sequence range of insert: amino acids 802-898 of SEQ

Purpose: phage display

Result: Interacts with coiled-coiled region of human SLK

15 Construct 3: PAK5 Dominant Negative

Vector: pCAN5

Insert: Full length coding sequence of human PAK5 containing the following mutation: K350,351A (Lys at aa positions 350 and 351 changed to Ala).

20 Purpose: to determine role of human PAK5 kinase activity in cell growth and transformation.

Result: Interferes with Ras transformation.

25 EXAMPLE 4: Generation of Specific Immunoreagents to STE20-Related Protein Kinases

Materials and Methods

Specific immunoreagents were raised in rabbits against KLH- or MAP-conjugated synthetic peptides corresponding to the human STE20-related kinases. C-terminal peptides were  
30 conjugated to KLH with glutaraldehyde, leaving a free C-terminus. Internal peptides were MAP-conjugated with a blocked N-terminus. Additional immunoreagents can also be generated by immunizing rabbits with the bacterially expressed



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GST-fusion proteins containing the cytoplasmic domains of each novel STK.

The various immune sera are first tested for reactivity and selectivity to recombinant protein, prior to testing for endogenous sources.

#### Western blots

Proteins in SDS PAGE are transferred to immobilon membrane. The washing buffer is PBST (standard phosphate-buffered saline pH 7.4 + 0.1% triton x 100). Blocking and antibody incubation buffer is PBST +5% milk. Antibody dilutions varied from 1:1000 to 1:2000.

#### RESULTS

Three SULU1 antisera (against both 539A and 540A) and two SULU3 antisera (542A) reacted specifically with the peptide antigens. Antisera binding was competable with peptide. Experiments with extracts from cells transfected with epitope-tagged SULU1 and SULU3 genes are underway.

Antisera against the PAK4 C-terminal peptide 554A reacted with purified Gst-PAK4 and detected a protein of the correct molecular weight from tissue culture cells. Specific immunoprecipitation experiments are ongoing to determine the reactivity with native protein.

Similar immunization and antisera testing experiments are underway for each of the other novel STE20-kinases.

STE20-related protein kinase peptide immunogens and their specificity in recognizing endogenous protein by Western blots or immunoprecipitations.

Protein	Sequence	Aa positions	Conj	West.	IP
STLK2	EKFQKCSADESP	405-416	KLH	Y	Y
STLK4	SISNSELFPTTDPVGT	252-267	KLH	Y	Y
SULU1	LDFPKEDYR	890-898	KLH	Y	Y
SULU1	HGDPRPEPRPTQ	409-420	KLH	Y	Y

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SULU3	PSTNRAGSLKDPEC	2-14	KLH	N	ND
SULU3	DPRTRASDPQSPPQVSRHK	411-429	KLH	ND	ND
PAK4	CLVPLIQLYRKQTSTC	666-680	KLH	ND	Y
PAK5	PLMRQNRTR	390-398	KLH	Y	Y
PAK5	SGDRRRAGPEKRPKSS	148-163	KLH	Y	Y
PAK5	(C) RRKSLVGTPYWMAPE	471-485	KLH	Y	ND

ND=not done yet

STE20-related protein kinase GST fusion protein immunogens and their specificity in recognizing endogenous protein by Western blots or immunoprecipitations.

5

Protein	domain	Aa positions	West.	IP
ZC1	Coiled-coil/pro/B/C	350-867	Y	Y
ZC1	B	615-732	Y	Y
ZC2	Coiled-coil /pro/B	348-762	ND	ND
ZC2	B	658-762	Y	Y
PAK4	Nterm	252-426	ND	ND
PAK4	Kinase/Cterm	350-681	ND	Y
PAK5	A/ Nterm	53-330	ND	ND
PAK5	A/Nterm	53-309	ND	ND

ND=not done yet

The 50kD STLK2 protein was expressed highly in several hematopoietic cell lines including Jurkat, pGL10, Ramos, A20, WEHI-231, K562, HEL and freshly isolated thymocytes from C57/BL6 mice. High levels of STLK2 expression were also detected in several tumor cell lines including Calu6, Colo205, LS180, MDAM231 and A549.

10

The 160 kD ZC1 protein was detected in Jurkat T cells, Colo205, HCT116, RIE-1, 293T, MDAMB231, and SK-MEL28.

15

The 170 kD ZC2 protein was detected in SK-Mel28 and UACC-62.

Elevated levels of the 64 kD PAK5 protein were confirmed in the breast cancer cell lines MDA-231 and MCF-7, and in the lung cancer cell line A549.

20

Example 5: Recombinant Expression and Biological Assays  
for STE20-related Protein Kinases

Materials and Methods

Transient Expression of the Ste20-related Kinases in  
Mammalian Cells

5 The pcDNA expression plasmids (10 µg DNA/100 mm plate) containing the STE20-related kinase constructs are introduced into 293 cells with lipofectamine (Gibco BRL). After 72 hours, the cells are harvested in 0.5 mL  
10 solubilization buffer (20 mM HEPES, pH 7.35, 150 mM NaCl, 10% glycerol, 1% Triton X-100, 1.5 mM MgCl<sub>2</sub>, 1 mM EGTA, 2 mM phenylmethylsulfonyl fluoride, 1 µg/mL aprotinin). Sample aliquots were resolved by SDS polyacrylamide gel electrophoresis (PAGE) on 6% acrylamide/0.5% bis-acrylamide  
15 gels and electrophoretically transferred to nitrocellulose. Non-specific binding was blocked by preincubating blots in Blotto (phosphate buffered saline containing 5% w/v non-fat dried milk and 0.2% v/v nonidet P-40 (Sigma)), and recombinant protein was detected using the various anti-peptide or anti-GST-fusion specific antisera.  
20

In Vitro Kinase Assays

Three days after transfection with the STE20-related kinase expression constructs, a 10 cm plate of 293 cells was  
25 washed with PBS and solubilized on ice with 2 mL PBSTDs containing phosphatase inhibitors (10 mM NaHPO<sub>4</sub>, pH 7.25, 150 mM NaCl, 1% Triton X-100, 0.5% deoxycholate, 0.1% SDS, 0.2% sodium azide, 1 mM NaF, 1 mM EGTA, 4 mM sodium orthovanadate, 1% aprotinin, 5 µg/mL leupeptin). Cell  
30 debris was removed by centrifugation (12000 x g, 15 min, 4 °C) and the lysate was precleared by two successive incubations with 50 µL of a 1:1 slurry of protein A sepharose for 1 hour each. One-half mL of the cleared

supernatant was reacted with 10  $\mu$ L of protein A purified kinase-specific antisera (generated from the GST fusion protein or antipeptide antisera) plus 50  $\mu$ L of a 1:1 slurry of protein A-sepharose for 2 hr at 4  $^{\circ}$ C. The beads were  
5 then washed 2 times in PBSTDS, and 2 times in HNTG (20 mM HEPES, pH 7.5/150 mM NaCl, 0.1% Triton X-100, 10% glycerol).

The immunopurified kinases on sepharose beads were resuspended in 20  $\mu$ L HNTG plus 30 mM  $MgCl_2$ , 10 mM  $MnCl_2$ , and  
10 20  $\mu$ Ci [ $\alpha^{32}P$ ]ATP (3000 Ci/mmol). The kinase reactions were run for 30 min at room temperature, and stopped by addition of HNTG supplemented with 50 mM EDTA. The samples were washed 6 times in HNTG, boiled 5 min in SDS sample buffer and analyzed by 6% SDS-PAGE followed by autoradiography.  
15 Phosphoamino acid analysis was performed by standard 2D methods on  $^{32}P$ -labeled bands excised from the SDS-PAGE gel.

Similar assays were performed on bacterially expressed GST-fusion constructs of the kinases.

20 ZC1 Assay buffer: 20 mM Tris pH 7.4, 200 mM NaCl, 0.5 mM DTT, 3 mM  $MgCl_2$ , 0.3 mM  $MnCl_2$ , 100 $\mu$ M  $^{32}P$ yATP.

Substrates: myelin basic protein (MBP) at 0.28 mg/mL and phosphorylated ZC1 peptide RTVGRRNTFIGT-PPYWMAPE at 17  $\mu$ M (bold underlined residue shows site of phosphorylation).

25 At higher concentrations of  $MgCl_2$  (3 mM), the activity of ZC1 (both full-length and recombinant kinase domain) is up to 10-fold greater towards exogenous substrate MBP. In contrast, the autophosphorylation and the phosphorylation of the activation loop peptide substrate are both inhibited.

30  $Mn^{++}$  does not inhibit the autophosphorylation and the peptide phosphorylation by the truncated kinase domain form. However, both the MBP phosphorylation,  $Mn^{++}$ -preferring activity AND the autophosphorylating,  $Mg^{++}$ -preferring

activity are eliminated with mutation of the ATP-binding lysine in ZC1 (Lys54Ala) indicating that both activities are attributable to the ZC1 kinase domain.

5        SULU1 Assay buffer: This buffer is identical to that for ZC1, except for 5 mM MgCl<sub>2</sub>. Under these conditions, other STE20 family members (PAK4, ZC1) were inhibited for autophosphorylation and required reducing the [Mn] to <0.3 mM for an efficient autophosphorylation reaction.

10        Substrates: MBP, phosvitin, or  $\alpha$ -casein at 0.28 mg/mL.

PAK4, PAK5 Assay Buffer: 20mM Hepes pH 7.2, 130 mM KCl, 10 mM MgCl<sub>2</sub>, 1 mM NaF, 20 mM B-glycerolphosphate, 0.5 mM DTT, 50  $\mu$ M ATP, 0.5  $\mu$ Ci <sup>32</sup>P $\gamma$ ATP.

15        Substrates: MBP at 0.28 mg/mL and peptide substrates derived from PAK5 activation loop at 2.5  $\mu$ M.

STLK2 Assay buffer: Similar to that described above, except for the inclusion of 5 mM MgCl<sub>2</sub>, 5 mM MnCl<sub>2</sub>, and 5  $\mu$ Ci <sup>32</sup>P $\gamma$ ATP.

20

#### Transformation (PAK experiments)

      Low-passage NIH3T3 fibroblasts displaying normal morphology (flat, non-refractile cellular morphology), as well as low rates of spontaneous transformation, were used in transformation assays. NIH3T3 cells were maintained in Dulbecco's modified Eagle's medium supplemented with 10% (v/v) fetal calf serum, penicillin (100 U/mL) and streptomycin (100 U/mL) and kept in an humidified incubator at 37 °C and 5% CO<sub>2</sub>.

30

      Cells were transfected with DNA-lipid complexes. As per manufacturer instructions, lipofectamine was utilized to transfect NIH3T3 cells. All transfections were with equal

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amounts of plasmid DNA (DNA from the appropriate expression vector without insert was used to give equivalent amounts of DNA per transfection). 1  $\mu$ g of activated allele of H-Ras was co-transfected with increasing amounts of various alleles of PAK5.

Foci were scored after 3 weeks by fixing 10 min in 10% methanol, 10% acetic acid for 10 min, followed by staining with 0.4% (w/v) crystal violet in 10% methanol for 10 min, and washing with deionized water and drying at room temperature.

Transfections, stimulations, and luciferase assays (ZC1 experiments)

Cells ( $10^7$ ) were transiently transfected by electroporation using a Gene Pulser (Bio-Rad Labs) with the setting of 960  $\mu$ F and 250 V. 20-40 hours later, transfected cells (about  $10^5$ ) were stimulated with various stimuli. After a 6-hour stimulation, cells were lysed, and luciferase activities were measured using the MicroLumatPlus (EG&G Berthold). (J. Exp. Med. 183:611-620, 1996, hereby incorporated by reference herein in its entirety including any drawings, tables, or figures.)

RESULTS

Protein expression and kinase activity of novel STE20-related protein kinases

Protein	Observed size (kD)	Predicted Size(kD)	In vitro Kinase activity	Endogenous Kinase activity
STLK2	50	46	Y	Y
STLK4	55	50	Y	ND
ZC1	160	140	Y	Y
ZC2	170	150	Y	Y
KHS2	ND	101	ND	ND
SULU1	119	105	Y	Y
SULU3	140	115	ND	Y

PAK4	80	75	Y	Y
PAK5	64	64	Y	Y

ZC1: Regulation of kinase activity

ZC1 is constitutively active as a full-length kinase when expressed either *in vitro* (TNT rabbit reticulocyte system) or in NIH 3T3, 293T, or H1299 tissue culture cells. The endogenously expressed kinase is also active when immunoprecipitated from carcinoma cell lines.

ZC1 signaling Pathways

Using human leukemic T cell line Jurkat as a model system, the impact of cotransfected wild-type ZC1 on the activation of two reporter genes, RE/AP-luciferase and NFkB luciferase, was examined. RE/AP is a composite in the IL-2 gene promoter containing both a NFkB-like site and an AP-1 site.

Optimal activation of both RE/AP-luciferase and NFkB-luciferase reporter genes in Jurkat T cells requires signals generated from stimulation of both T cell receptor and the costimulator receptor CD28. Cotransfection of wild-type ZC1 with either the RE/AP-luciferase or the NFkB-luciferase reporter results in the activation of RE/AP or NFkB when costimulated with the anti-T cell receptor monoclonal antibody or the pharmacological reagents PMA and ionomycin that bypass proximal T cell receptor. No activation was seen when costimulated with an anti-CD28 monoclonal antibody.

These results suggest that wild-type ZC1, when overexpressed, was replacing a CD28-specific signal to activate RE/AP or NFkB. These results imply that ZC1 is involved in the CD28 signaling pathway. Since NFkB is one of the major pathways also activated by the pro-inflammatory

cytokine TNF- $\alpha$  signaling, it is also likely that ZC1 may be a component in the TNF- $\alpha$  signaling pathways.

#### PAK5: Design of specific peptide substrates

To aid in the development of *in vitro* kinase assays for screening small molecule libraries to identify specific inhibitors, the search for specific peptide substrates for PAK5 was undertaken.

The rationale used to design such peptides is based on the hypothesis that upon binding activated small G protein, PAK5 undergoes a conformational change that results in derepression of its kinase activity followed by autophosphorylation on the activation loop resulting in a fully active kinase. The site of autophosphorylation for related family members has been identified by biochemical and/or genetic means (e.g. Wu, C, et al. J.Biol.Chem 270:15984-15992 and Szczepanowska, et al. Proc.Natl.Acad.Sci 94, 8503-8508, 1997). Specific peptide substrates for PAK5 were designed from the sequence of the activation loop of this kinase.

An activation loop PAK5 peptide phosphorylated on the Thr residue of the TPY motif served as a high-affinity substrate for PAK5.

#### PAK5 activation loop peptides as kinase substrates

Peptide #	Kinase	Sequence	Aa	SEQ ID	Kinase	substrate
1	PAK5	(C)RRKSLVG <b>T</b> PYWMAPE	471-485	102	PAK5	yes
2	PAK5	(C)RRKSLVG <b>T</b> PYWMAPE	471-485	102	PAK5	yes
3	PAK5	(C)RRKSLVG <b>T</b> PYWMAPE	471-485	102	PAK5	no
4	KHS1	KRK <b>S</b> FIGTPYWMAPE	171-185	U77129	PAK5	yes
5	STLK2	KRNTFVG <b>T</b> PFWMAPE	175-189	5	PAK5	poor
6	SULU1	PANSFVG <b>T</b> PYWMAPE	174-188	22	PAK5	poor
7	ZC1	RRNTFIG <b>T</b> PYWMAPE	184-198	13	PAK5	poor
8	ZC1	RRNTFIG <b>T</b> PYWMAPE	184-198	13	PAK5	poor
9	STLK4	RNKVRK <b>T</b> FGTPCWMAPE	66-83	7	PAK5	poor
10	PAK5	(C)RRKSLVG <b>T</b> PYWMAPE	471-485	102	PAK4	yes

Note: underlined/ bold residue was phosphorylated



Peptide #	Kinase	Notes
1	PAK5	Equally well as MBB
2	PAK5	High Km for PAK5 (1-10 $\mu$ M)
3	PAK5	S is the site of phosphorylation
4	KHS1	Similar to peptide 1
5	STLK2	
6	SULU1	
7	ZC1	
8	ZC1	Better than 7
9	STLK4	
10	PAK5	Same Km as phosph. by PAK5

#### PAK5: Transformation

5 Transformation of low-passage NIH3T3 cells by ras in the presence or absence of various alleles of PAK5 showed that the dominant negative, kinase-dead allele of PAK5 was able to block ras transformation of NIH3T3 cells. Thus, PAK5 activity is required for ras transformation of NIH3T3 cells.

10 Inhibition of PAK5 activity may have therapeutic value as an anti-proliferative agent for treating cancer.

#### PAK4 and PAK5: interaction with Cdc42

15 PAK 4 interacts with CDC42 small G-protein but not Rac, RhoA, or Ras as determined by co-transfection of recombinant genes and detection by kinase assays. PAK5 also interacts with Cdc42. Coding sequences of activated alleles of small G proteins (ras, Cdc42, Rac, Rho) tagged with a Myc epitope were transiently expressed in 293T cells, various alleles of  
20 35S-labeled PAK5 tagged with HA epitope were expressed in vitro with the reticulocyte (TNT) system.

Example 6: Chromosomal Localization of Ste20-Related  
Protein Kinases

Materials And Methods

STE20 protein kinases STLK3, STLK4, ZC1, ZC2, ZC3,  
5 KHS2, SULU1, PAK4, and PAK5 were mapped using the GeneBridge  
4 Radiation Hybrid Panel, RH02.05 (Research Genetics). The  
GeneBridge 4 Panel consists of 91 hybrid panel samples, in  
addition to one human positive control (HFL), and one  
hamster negative control (A23). The standard reaction  
10 conditions used to test and conduct PCR reactions using the  
GeneBridge 4 Panel are available from Research Genetics.

Oligonucleotide sequences (all 5' to 3') used for PCR  
mapping were:

15	STLK3: CTCCCATTTCTAGCAAAATCA,	AGAGGCAGTATTGTCAGATGTA
	STLK4: CCACACATGCGTATCTCTGTTG,	TTGCTAGAATTCACATCAGGTACA
	ZC1: ATCCCTGGATCACACTGCTTCT,	CAAGGTGTTCTTTGCCTCTGTT
	ZC2: AGATGGACTGTACTGGGAGGG,	AGAAGAGCACTTGGCACTTATC
	ZC3: CATCATGAACTGGTGACGGG,	CCAGTGAAATCAAACCAGTAAAA
20	SULU1: CAAAACCTGGCCGTCTCTTCTATT,	ATTTGTGCTACTGGGATTCTGTG
	KHS2: GAATAGCGGTACCATGATAGAATA,	TACCAAAAAGAGCCAAAAGTGTG
	PAK4: CTCAGTATTCTCTCAAAGATTG,	GATGTTCTCTCCATTCTGTAAAG
	PAK5: CATCACTGGAAGTCTGCAGTG,	CAGGTGCAGTAGTCATTTGC

25 Positive reactions were assigned a score of "1",  
negative reactions are assigned a score of "0", and  
ambiguous reactions are assigned a score of "2". Results  
were submitted to the Whitehead Institute  
(www@genome.wi.mit.edu) for position analysis. Chromosomal  
30 localizations for ZC4, SULU3, STLK2, STLK5 and STLK6 were  
available publicly (for example, from Unigene). The  
chromosomal locations of GEK2 and STLK7 have not been  
determined.

STLK2_h	Xq25-27.1	(Public)
STLK3	2q31.3	(Sugen)
STLK4_h	3p22.3-p22.2	(Sugen)
STLK5_h	17q23.2-24.2	(Public)

STLK6_h	2q32.2 -q33.3	(Public)
STLK7_h	NA	
ZC1_h	2p11.2	(Sugen)
ZC2_h	3q26.31-3q26.32	(Sugen)
ZC3_h	17p13.2-13.3	(Sugen)
ZC4_h	Xq22	(Public)
KHS2_h	2p22-2p22.2	(Sugen)
SULU1_h	12q24.21	(Sugen)
SULU3_h	17p11.2	(Public)
GEK2_h	NA	
PAK4_h	15q14	(Sugen)
PAK5_h	19q13.2-q13.3	(Sugen)

Many of the STE 20 kinases were mapped to regions associated with various human cancers, as shown below.

The regions were also cross-checked with the Mendelian Inheritance in Man database, which tracks genetic information for many human diseases, including cancer. References for association of the mapped sites with chromosomal abnormalities found in human cancer can be found in: Knuutila, et al., Am J Pathol, 1998, 152:1107-1123, hereby incorporated herein by reference in its entirety including any figures, tables, or drawings. Association of these mapped regions with other diseases is documented in the Online Mendelian Inheritance in Man (OMIM) (<http://www.ncbi.nlm.nih.gov/htbin-post/Omim>).

15

STLK2\_h, Xq25-27.1, (Public)

Osteosarcoma, Xq25-qter, 2 of 31.

Lymphoproliferative syndrome, X-linked (OMIM No. 308240)

human STLK3, 2q31.3, (Sugen)

20

Squamous cell carcinoma of Head and Neck, 3 of 30.

STLK4\_h, 3p22.3-p22.2, (Sugen)

Mantle cell lymphoma 3p14-p22 1 of 27

Squamous cell carcinoma of Head and Neck 3p22-p24 1 of 14

25

Cardiomyopathy, dilated (OMIM 601154)

STLK5\_h, 17q23.2-24.2, (Public)

- Cervical cancer, 17q, 1 of 30  
Gastroesophageal junction adenocarcinoma xenograft, 17q, 1  
5 of 5  
Breast carcinoma, 17q12-qter, 1 of 16  
Bladder carcinoma, 17q22-q23, 1 of 14  
Breast carcinoma, 17q22-q25, 8 of 101  
Non-small cell lung cancer, 17q24-q25, 6 of 50  
10 Testis, 17q24-qter, 2 of 11  
Malignant peripheral nerve sheath tumors, 17q24-qter, 5 of 7  
Alzheimer disease, susceptibility to (OMIM 106180)

STLK6\_h, 2q32.2 -q33.3, (Public)

- 15 Non-small cell lung cancer, 2q31-q32, 1 of 50  
Squamous cell carcinoma of Head and Neck, 2q31-q33, 3 of 30  
Small cell lung cancer, 2q32-q35, 1 of 22

ZC1\_h, 2p11.2, (Sugen)

- 20 non-small cell lung cancer, 2pter-q13, 1 of 10  
non-small cell lung cancer, 2pter-q21, 1 of 10  
Pulmonary alveolar proteinosis, congenital (OMIM 178640).

ZC2\_h, 3q26.31-3q26.32, (Sugen)

- 25 Non-small cell lung cancer, 3q26.1-q26.3, 26 of 103  
Cervical cancer, 3q26.1-q27, 4 of 30  
Small cell lung cancer, 3q26.3-qter, 3 of 35  
Squamous cell carcinoma of Head and Neck, 3q26.3-qter, 3 of  
13  
30 Marginal zone B-cell lymphoma, 3q26-q27, 1 of 25  
Parosteal osteosarcoma, 3q26-q28, 1 of 1  
Gastrointestinal stromal tumor, 3q26-q29, 1 of 16  
Mantle cell lymphoma, 3q26-q29, 1 of 5

ZC3\_h 17p13.2-13.3 (Sugen)

Malignant fibrous histiocyctoma of soft tissue, 17p, 2 of 58

Leiomyosarcoma, 17p, 7 of 29

5 Non-small cell lung cancer, 17p, 1 of 50

ZC4\_h, Xq22, (Public)

Diffuse large cell lymphoma, Xq22-ter, 1 of 32

Deafness, X-linked 1, progressive. (OMIM 304700).

10

KHS2\_h, 2p22-2p22.2, (Sugen)

Synovial sarcoma, 2p21-q14, 1\_of\_67

Follicular lymphoma, 2p22-p24, 1\_of\_46

Colorectal cancer, hereditary, nonpolyposis, type 1, Ovarian

15 cancer (MSH2, COCA1, FCC1). (OMIM 120435).

SULU1\_h, 12q24.21 (Sugen)

Neuroglial tumors, 12q22-qter, 1\_of\_15

Gastroesophageal junction adenocarcinoma, 12q23-qter, 1 of

20 5.

Non-small cell lung cancer, 12q24.1-24.3, 2 of 50.

SULU3\_h 17p11.2 (Public)

Malignant fibrous histiocyctoma of soft tissue, 17p, 2\_of\_58

25 Leiomyosarcoma, 17p, 7\_of\_29

non-small cell lung cancer, 17p, 1\_of\_50

Diffuse large cell lymphoma, 17p11.2, 1\_of\_32

Osteosarcoma, 17p11.2-p12, 4\_of\_31

30 PAK4\_h: 15q14 (Sugen)

Schizophrenia, (OMIM 118511).

PAK5\_h: 19q13.2-q13.3 (Sugen)

Follicular lymphoma, 19q13, 1 of 46\*

Mantle cell lymphoma, 19q13, 1 of 5

Hepatocellular carcinoma, 19q13.1, 2 of 50

5 Small cell lung cancer, 19q13.1, 10 of 35

Breast carcinoma, 19q13.1-qter, 1 of 33

cervical cancer, 19q13.1-qter, 1 of 30

Testis, 19q13.1-qter, 1 of 11

Chondrosarcoma, 19q13.2, 1 of 29

10 Malignant fibrous histiocytoma of soft tissue, 19q13.2-qter,  
2 of 58

Non-small cell lung cancer, 19qcen-q13.3, 6 of 104

15 Example 7: Demonstration Of Gene Amplification By  
Southern Blotting

Materials and Methods

Nylon membranes were purchased from Boehringer Mannheim. Denaturing solution contains 0.4 M NaOH and 0.6 M NaCl. Neutralization solution contains 0.5 M Tris-HCL, pH 7.5 and 1.5 M NaCl. Hybridization solution contains 50%  
20 formamide, 6X SSPE, 2.5X Denhardt's solution, 0.2 mg/mL denatured salmon DNA, 0.1 mg/mL yeast tRNA, and 0.2 % sodium dodecyl sulfate. Restriction enzymes were purchased from Boehringer Mannheim. Radiolabeled probes were prepared  
25 using the Prime-it II kit by Stratagene. The beta actin DNA fragment used for a probe template was purchased from Clontech.

Genomic DNA was isolated from 20 different tumor cell lines: MCF-7, MDA-MB-231, Calu-6, A549, HCT-15, HT-29, Colo  
30 205, LS-180, DLD-1, HCT-116, PC3, CAPAN-2, MIA-PaCa-2, PANC-1, AsPc-1, BxPC-3, OVCAR-3, SKOV3, SW 626 and PA-1, and from two normal cell lines: human mammary epithelial cells and human umbilical vein endothelial cells.

A 10 µg aliquot of each genomic DNA sample was digested with EcoR I restriction enzyme and a separate 10 µg sample was digested with Hind III restriction enzyme. The restriction-digested DNA samples were loaded onto a 0.7% agarose gel and, following electrophoretic separation, the DNA was capillary-transferred to a nylon membrane by standard methods (Sambrook, J. et al (1989) Molecular Cloning: A Laboratory Manual, Cold Spring Harbor Laboratory).

#### PAK5 Amplicon:

A 600 base pair fragment (EcoR I - Sac I) of the PAK5 gene was used as a template for a radiolabeled DNA probe which was hybridized to the blots at 42 °C for 48 hours in hybridization solution using standard methods (supra). The blots were exposed to a phosphorimager screen for 4 days, then scanned and analyzed using a Molecular Dynamics Storm 840 phosphorimager. The relative mass and gene copy number values of the PAK5 DNA fragments were calculated from the band density values obtained. The blots were re-hybridized with a radiolabeled probe copied from a fragment of human beta actin DNA and developed as above to confirm the sample mass loading equivalency.

#### RESULTS

The PAK5 gene was determined to exhibit 3-fold amplification compared to the normal DNA copy number in PANC-1 (pancreatic epithelioid carcinoma) and OVCAR-3 (ovarian adenocarcinoma) human cell lines, and approximately 2 times the normal copy number in the BxPC-3 (primary pancreatic adenocarcinoma) human cell line.

Similar Southern analyses can be performed for other STE20 kinases.

Example 8: Detection Of Protein-Protein Interaction  
Through Phage Display

Materials And Methods

5           Phage display provides a method for isolating molecular  
interactions based on affinity for a desired bait. cDNA  
fragments cloned as fusions to phage coat proteins are  
displayed on the surface of the phage. Phage(s) interacting  
with a bait are enriched by affinity purification and the  
10       insert DNA from individual clones is analyzed.

T7 Phage Display Libraries

          All libraries were constructed in the T7Select1-1b  
vector (Novagen) according to the manufacturer's directions.

15

Bait Presentation

          Protein domains to be used as baits were generated as  
C-terminal fusions to GST and expressed in *E. coli*.  
Peptides were chemically synthesized and biotinylated at the  
20       N-terminus using a long chain spacer biotin reagent.

Selection

          Aliquots of refreshed libraries ( $10^{10}$ - $10^{12}$  pfu)  
supplemented with PanMix and a cocktail of *E. coli*  
inhibitors (Sigma P-8465) were incubated for 1-2 hrs at room  
25       temperature with the immobilized baits. Unbound phage was  
extensively washed (at least 4 times) with wash buffer.

          After 3-4 rounds of selection, bound phage was eluted  
in 100  $\mu$ L of 1% SDS and plated on agarose plates to obtain  
single plaques.

30

Identification of insert DNAs

          Individual plaques were picked into 25  $\mu$ L of 10 mM EDTA  
and the phage was disrupted by heating at 70 °C for 10 min.



2  $\mu$ L of the disrupted phage were added to 50  $\mu$ L PCR reaction mix. The insert DNA was amplified by 35 rounds of thermal cycling (94oC, 50sec; 50oC, 1min; 72oC, 1min).

5     Composition of Buffer

10x PanMix

5% Triton X100

10% non-fat dry milk (Carnation)

10 mM EGTA

10     250 mM NaF

250  $\mu$ g/mL Heparin (sigma)

250  $\mu$ g/mL sheared, boiled salmon sperm DNA (sigma)

0.05% Na azide

Prepared in PBS

15

Wash Buffer

PBS supplemented with:

0.5% NP-40

25  $\mu$ l g/mL heparin

20

**PCR reaction mix**

1.0 mL       10x PCR buffer (Perkin-Elmer, with 15 mM Mg)

0.2 mL each dNTPs (10 mM stock)

0.1 mL       T7UP primer (15 pmol/ $\mu$ L) GGAGCTGTCGTATTCCAGTC

25     0.1 mL       T7DN primer (15 pmol/ $\mu$ L) AACCCCTCAAGACCCGTTTAG

0.2 mL       25 mM MgCl<sub>2</sub> or MgSO<sub>4</sub> to compensate for EDTA

Q.S. to 10 mL with distilled water

Add 1 unit of Taq polymerase per 50  $\mu$ L reaction

30     LIBRARY: T7 Select1-H441

RESULTS

## Phage display baits and interactors

Bait	Domain	Aa	Patent SEQ ID	CDNA library	Interactor	Sequence Range & SEQ ID
SULU1	Coiled-coil2	752-898	22	H441	GEK2 cc dom (1)	677-820 SEQ #26
SULU3	Coiled-coil2	755-898	23	H441	SLK isoform	M83780

(1) SULU1 ccl also interacted to a lesser extent with the coiled-coil domain of an SLK isoform.

The phage display data suggest potential interactions of SULU3 with SLK and SULU1 with GEK2 through their coiled-coil domains. Therefore two members of the SULU subfamily of STE20 kinases interact with two members of a separate STE20 family, the prototype being SLK.

These results suggest a specificity in the interaction, and imply that these STE20 kinases may interact with each other through homo- and hetero-dimerization. Alternatively SULU-related kinases could act immediately up- or down-stream of the SLK-related kinases in a signaling cascade.

One skilled in the art would readily appreciate that the present invention is well adapted to carry out the objects and obtain the ends and advantages mentioned, as well as those inherent therein. The molecular complexes and the methods, procedures, treatments, molecules, specific compounds described herein are presently representative of preferred embodiments are exemplary and are not intended as limitations on the scope of the invention. Changes therein and other uses will occur to those skilled in the art which are encompassed within the spirit of the invention are defined by the scope of the claims.

It will be readily apparent to one skilled in the art that varying substitutions and modifications may be made to

the invention disclosed herein without departing from the scope and spirit of the invention.

5 All patents and publications mentioned in the specification are indicative of the levels of those skilled in the art to which the invention pertains.

The invention illustratively described herein suitably may be practiced in the absence of any element or elements, limitation or limitations which is not specifically disclosed herein. Thus, for example, in each instance  
10 herein any of the terms "comprising", "consisting essentially of" and "consisting of" may be replaced with either of the other two terms. The terms and expressions which have been employed are used as terms of description and not of limitation, and there is no intention that in the  
15 use of such terms and expressions of excluding any equivalents of the features shown and described or portions thereof, but it is recognized that various modifications are possible within the scope of the invention claimed.

In particular, although some formulations described  
20 herein have been identified by the excipients added to the formulations, the invention is meant to also cover the final formulation formed by the combination of these excipients. Specifically, the invention includes formulations in which one to all of the added excipients undergo a reaction during  
25 formulation and are no longer present in the final formulation, or are present in modified forms.

In addition, where features or aspects of the invention are described in terms of Markush groups, those skilled in the art will recognize that the invention is also thereby  
30 described in terms of any individual member or subgroup of members of the Markush group. For example, if X is described as selected from the group consisting of bromine,

chlorine, and iodine, claims for X being bromine and claims for X being bromine and chlorine are fully described.

Other embodiments are within the following claims.

## SEQUENCE LISTING

&lt;110&gt; SUGEN, INC.

&lt;120&gt; STE20-RELATED PROTEIN KINASES

&lt;130&gt; 240/300-PCT

&lt;140&gt; TO BE ASSIGNED

&lt;141&gt; Herewith

&lt;150&gt; US 60/081,784

&lt;151&gt; 1998-04-14

&lt;160&gt; 147

&lt;170&gt; FastSEQ for Windows Version 3.0

&lt;210&gt; 1

&lt;211&gt; 3268

&lt;212&gt; DNA

&lt;213&gt; Mammalian (Human) STK2

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&lt;212&gt; DNA

&lt;213&gt; Mammalian (Human) STLK3

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&lt;212&gt; DNA

&lt;213&gt; Mammalian (Human) STLK4

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Val Val Ala Ile Lys Ile Ile Asp Leu Glu Glu Ala Glu Asp Glu Ile  
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 Glu Asp Ile Gln Gln Glu Ile Thr Val Leu Ser Gln Cys Asp Ser Ser  
 65 70 75 80  
 Tyr Val Thr Lys Tyr Tyr Gly Ser Tyr Leu Lys Gly Ser Lys Leu Trp  
 85 90 95  
 Ile Ile Met Glu Tyr Leu Gly Gly Gly Ser Ala Leu Asp Leu Leu Arg  
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 Ala Gly Pro Phe Asp Glu Phe Gln Ile Ala Thr Met Leu Lys Glu Ile  
 115 120 125  
 Leu Lys Gly Leu Asp Tyr Leu His Ser Glu Lys Lys Ile His Arg Asp  
 130 135 140  
 Ile Lys Ala Ala Asn Val Leu Leu Ser Glu Gln Gly Asp Val Lys Leu  
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 Ala Asp Phe Gly Val Ala Gly Gln Leu Thr Asp Thr Gln Ile Lys Arg  
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 Asn Thr Phe Val Gly Thr Pro Phe Trp Met Ala Pro Glu Val Ile Gln  
 180 185 190  
 Gln Ser Ala Tyr Asp Ser Lys Ala Asp Ile Trp Ser Leu Gly Ile Thr  
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 Ala Ile Glu Leu Ala Lys Gly Glu Pro Pro Asn Ser Asp Met His Pro  
 210 215 220  
 Met Arg Val Leu Phe Leu Ile Pro Lys Asn Asn Pro Pro Thr Leu Val  
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 Gly Asp Phe Thr Lys Ser Phe Lys Glu Phe Ile Asp Ala Cys Leu Asn  
 245 250 255  
 Lys Asp Pro Ser Phe Arg Pro Thr Ala Lys Glu Leu Leu Lys His Lys  
 260 265 270  
 Phe Ile Val Lys Asn Ser Lys Lys Thr Ser Tyr Leu Thr Glu Leu Ile  
 275 280 285  
 Asp Arg Phe Lys Arg Trp Lys Ala Glu Gly His Ser Asp Asp Glu Ser  
 290 295 300  
 Asp Ser Glu Gly Ser Asp Ser Glu Ser Thr Ser Arg Glu Asn Asn Thr  
 305 310 315 320  
 His Pro Glu Trp Ser Phe Thr Thr Val Arg Lys Lys Pro Asp Pro Lys  
 325 330 335  
 Lys Val Gln Asn Gly Ala Glu Gln Asp Leu Val Gln Thr Leu Ser Cys  
 340 345 350

Leu Ser Met Ile Ile Thr Pro Ala Phe Ala Glu Leu Lys Gln Gln Asp  
 355 360 365

Glu Asn Asn Ala Ser Arg Asn Gln Ala Ile Glu Glu Leu Glu Lys Ser  
 370 375 380

Ile Ala Val Ala Glu Ala Ala Cys Pro Gly Ile Thr Asp Lys Met Val  
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Lys Lys Leu Ile Glu Lys Phe Gln Lys Cys Ser Ala Asp Glu Ser Pro  
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<210> 6  
 <211> 516  
 <212> PRT  
 <213> Mammalian (Human) STLK3

<400> 6

Thr Ala Ala Pro Ala Pro Ala Ala Pro Ala Ala Pro Ala Pro Ala Pro  
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Ala Pro Ala Pro Ala Ala Gln Ala Val Gly Trp Pro Ile Cys Arg Asp  
 20 25 30

Ala Tyr Glu Leu Gln Glu Val Ile Gly Ser Gly Ala Thr Ala Val Val  
 35 40 45

Gln Ala Ala Leu Cys Lys Pro Arg Gln Glu Arg Val Ala Ile Lys Arg  
 50 55 60

Ile Asn Leu Glu Lys Cys Gln Thr Ser Met Asp Glu Leu Leu Lys Glu  
 65 70 75 80

Ile Gln Ala Met Ser Gln Cys Ser His Pro Asn Val Val Thr Tyr Tyr  
 85 90 95

Thr Ser Phe Val Val Lys Asp Glu Leu Trp Leu Val Met Lys Leu Leu  
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Ser Gly Gly Ser Met Leu Asp Ile Ile Lys Tyr Ile Val Asn Arg Gly  
 115 120 125

Glu His Lys Asn Gly Val Leu Glu Glu Ala Ile Ile Ala Thr Ile Leu  
 130 135 140

Lys Glu Val Leu Glu Gly Leu Asp Tyr Leu His Arg Asn Gly Gln Ile  
 145 150 155 160

His Arg Asp Leu Lys Ala Gly Asn Ile Leu Leu Gly Glu Asp Gly Ser  
 165 170 175

Val Gln Ile Ala Asp Phe Gly Val Ser Ala Phe Leu Ala Thr Gly Gly  
 180 185 190  
 Asp Val Thr Arg Asn Lys Val Arg Lys Thr Phe Val Gly Thr Pro Cys  
 195 200 205  
 Trp Met Ala Pro Glu Val Met Glu Gln Val Arg Gly Tyr Asp Phe Lys  
 210 215 220  
 Ala Asp Met Trp Ser Phe Gly Ile Thr Ala Ile Glu Leu Ala Thr Gly  
 225 230 235 240  
 Ala Ala Pro Tyr His Lys Tyr Pro Pro Met Lys Val Leu Met Leu Thr  
 245 250 255  
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 260 265 270  
 Met Met Lys Lys Tyr Gly Lys Ser Phe Arg Lys Leu Leu Ser Leu Cys  
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 Cys Lys Phe Phe Gln Lys Ala Lys Asn Arg Glu Tyr Leu Ile Glu Lys  
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 Leu Leu Thr Arg Thr Pro Asp Ile Ala Gln Arg Ala Lys Lys Val Arg  
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 Arg Val Pro Gly Ser Ser Gly His Leu His Lys Thr Glu Asp Gly Asp  
 340 345 350  
 Trp Glu Trp Ser Asp Asp Glu Met Asp Glu Lys Ser Glu Glu Gly Lys  
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 Ala Ala Phe Ser Gln Glu Lys Ser Arg Arg Val Lys Glu Glu Asn Pro  
 370 375 380  
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 385 390 395 400  
 Ser Val His Asp Ser Gln Gly Pro Pro Asn Ala Asn Glu Asp Tyr Arg  
 405 410 415  
 Glu Ala Ser Ser Cys Ala Val Asn Leu Val Leu Arg Leu Arg Asn Ser  
 420 425 430  
 Arg Lys Glu Leu Asn Asp Ile Arg Phe Glu Phe Thr Pro Gly Arg Asp  
 435 440 445  
 Thr Ala Asp Gly Val Ser Gln Glu Leu Phe Ser Ala Gly Leu Val Asp  
 450 455 460  
 Gly His Asp Val Val Ile Val Ala Ala Asn Leu Gln Lys Ile Val Asp

465                      470                      475                      480

Asp Pro Lys Ala Leu Lys Thr Leu Thr Phe Lys Leu Ala Ser Gly Cys  
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Asp Gly Ser Glu Ile Pro Asp Glu Val Lys Leu Ile Gly Phe Ala Gln  
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Leu Ser Val Ser  
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<210> 7  
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 <212> PRT  
 <213> Mammalian (Human) STLK4

<220> .  
 <223> "Xaa" stands for any amino acid.

<400> 7

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Val Leu Glu Gly Leu Glu Tyr Leu His Lys Xaa Gly Gln Ile His Arg  
                                  20                      25                      30

Asp Val Lys Ala Gly Asn Ile Leu Xaa Gly Glu Asp Gly Ser Val Gln  
                                  35                      40                      45

Ile Ala Asp Phe Gly Val Ser Ala Phe Leu Ala Thr Gly Gly Asp Ile  
                                  50                      55                      60

Thr Arg Asn Lys Val Arg Lys Thr Phe Val Gly Thr Pro Cys Trp Met  
 65                      70                      75                      80

Ala Pro Glu Val Met Glu Gln Val Arg Gly Tyr Asp Phe Lys Ala Asp  
                                  85                      90                      95

Ile Trp Ser Phe Gly Ile Thr Ala Ile Glu Leu Ala Thr Gly Ala Ala  
                                  100                      105                      110

Pro Tyr His Lys Tyr Pro Pro Met Lys Val Leu Met Leu Thr Leu Gln  
                                  115                      120                      125

Asn Asp Pro Pro Ser Leu Glu Thr Gly Val Gln Asp Lys Glu Met Leu  
                                  130                      135                      140

Lys Lys Tyr Gly Lys Ser Phe Arg Lys Met Ile Ser Leu Cys Leu Gln  
 145                      150                      155                      160

Lys Asp Pro Glu Lys Arg Pro Thr Ala Ala Glu Leu Leu Arg His Lys  
                                  165                      170                      175

10

Phe Phe Gln Lys Ala Lys Asn Lys Glu Phe Leu Gln Glu Lys Thr Leu  
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 Gln Arg Ala Pro Thr Ile Ser Glu Arg Ala Lys Lys Val Arg Arg Val  
 195 200 205  
 Pro Gly Ser Ser Gly Arg Leu His Lys Thr Glu Asp Gly Gly Trp Glu  
 210 215 220  
 Trp Ser Asp Asp Glu Phe Asp Glu Glu Ser Glu Glu Gly Lys Ala Ala  
 225 230 235 240  
 Ile Ser Gln Leu Arg Ser Pro Arg Val Lys Glu Ser Ile Ser Asn Ser  
 245 250 255  
 Glu Leu Phe Pro Thr Thr Asp Pro Val Gly Thr Leu Leu Gln Val Pro  
 260 265 270  
 Glu Gln Ile Ser Ala His Leu Pro Gln Pro Ala Gly Gln Ile Ala Thr  
 275 280 285  
 Gln Pro Thr Gln Val Ser Leu Pro Pro Thr Ala Glu Pro Ala Lys Thr  
 290 295 300  
 Ala Gln Ala Leu Ser Ser Gly Ser Gly Ser Gln Glu Thr Lys Ile Pro  
 305 310 315 320  
 Ile Ser Leu Val Leu Arg Leu Arg Asn Ser Lys Lys Glu Leu Asn Asp  
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 Ile Arg Phe Glu Phe Thr Pro Gly Arg Asp Thr Ala Glu Gly Val Ser  
 340 345 350  
 Gln Glu Leu Ile Ser Ala Gly Leu Val Asp Gly Arg Asp Leu Val Ile  
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 Val Ala Ala Asn Leu Gln Lys Ile Val Glu Glu Pro Gln Ser Asn Arg  
 370 375 380  
 Ser Val Thr Phe Lys Leu Ala Ser Gly Val Glu Gly Ser Asp Ile Pro  
 385 390 395 400  
 Asp Asp Gly Lys Leu Ile Gly Phe Ala Gln Leu Ser Ile Ser  
 405 410

&lt;210&gt; 8

&lt;211&gt; 274

&lt;212&gt; PRT

&lt;213&gt; Mammalian (Human) STLK5

&lt;400&gt; 8

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Tyr Ile Leu Gln Gly Val Leu Lys Ala Leu Asp Tyr Ile His His Met  
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 Gly Tyr Val His Arg Ser Val Lys Ala Ser His Ile Leu Ile Ser Val  
 35 40 45  
 Asp Gly Lys Val Tyr Leu Ser Gly Leu Arg Ser Asn Leu Ser Met Ile  
 50 55 60  
 Ser His Gly Gln Arg Gln Arg Val Val His Asp Phe Pro Lys Tyr Ser  
 65 70 75 80  
 Val Lys Val Leu Pro Trp Leu Ser Pro Glu Val Leu Gln Gln Asn Leu  
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 Gln Gly Tyr Asp Ala Lys Ser Asp Ile Tyr Ser Val Gly Ile Thr Ala  
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 Cys Glu Leu Ala Asn Gly His Val Pro Phe Lys Asp Met Pro Ala Thr  
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 Gln Met Leu Leu Glu Lys Leu Asn Gly Thr Val Pro Cys Leu Leu Asp  
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 Thr Ser Thr Ile Pro Ala Glu Glu Leu Thr Met Ser Pro Ser Arg Ser  
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 Val Ala Asn Ser Gly Leu Ser Asp Ser Leu Thr Thr Ser Thr Pro Arg  
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 Pro Ser Asn Gly Asp Ser Pro Ser His Pro Tyr His Arg Thr Phe Ser  
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 Pro His Phe His His Phe Val Glu Gln Cys Leu Gln Arg Asn Pro Asp  
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 Ala Arg Pro Ser Ala Ser Thr Leu Leu Asn His Ser Phe Phe Lys Gln  
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 Ile Lys Arg Arg Ala Ser Glu Ala Leu Pro Glu Leu Leu Arg Pro Val  
 225 230 235 240  
 Thr Pro Ile Thr Asn Phe Glu Gly Ser Gln Ser Gln Asp His Ser Gly  
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 Glu Phe

&lt;210&gt; 9

&lt;211&gt; 3798

&lt;212&gt; DNA

&lt;213&gt; Mammalian (Human) ZC1

&lt;400&gt; 9

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&lt;210&gt; 10

&lt;211&gt; 4055

&lt;212&gt; DNA

&lt;213&gt; Mammalian (Human) ZC2

&lt;400&gt; 10

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&lt;211&gt; 4133

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&lt;213&gt; Mammalian (Human) ZC3

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Asn	Gly	Thr	Tyr	Gly	Gln	Val	Tyr	Lys	Gly	Arg	His	Val	Lys	Thr	Gly

17

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Gln Leu Ala Ala Ile Lys Val Met Asp Val Thr Glu Asp Glu Glu Glu		
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Glu Ile Lys Leu Glu Ile Asn Met Leu Lys Lys Tyr Ser His His Arg		
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Asn Ile Ala Thr Tyr Tyr Gly Ala Phe Ile Lys Lys Ser Pro Pro Gly		
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His Asp Asp Gln Leu Trp Leu Val Met Glu Phe Cys Gly Ala Gly Ser		
	100	105 110
Ile Thr Asp Leu Val Lys Asn Thr Lys Gly Asn Thr Leu Lys Glu Asp		
	115	120 125
Trp Ile Ala Tyr Ile Ser Arg Glu Ile Leu Arg Gly Leu Ala His Leu		
	130	135 140
His Ile His His Val Ile His Arg Asp Ile Lys Gly Gln Asn Val Leu		
145	150	155 160
Leu Thr Glu Asn Ala Glu Val Lys Leu Val Asp Phe Gly Val Ser Ala		
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Gln Leu Asp Arg Thr Val Gly Arg Arg Asn Thr Phe Ile Gly Thr Pro		
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Tyr Trp Met Ala Pro Glu Val Ile Ala Cys Asp Glu Asn Pro Asp Ala		
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Thr Tyr Asp Tyr Arg Ser Asp Leu Trp Ser Cys Gly Ile Thr Ala Ile		
	210	215 220
Glu Met Ala Glu Gly Ala Pro Pro Leu Cys Asp Met His Pro Met Arg		
225	230	235 240
Ala Leu Phe Leu Ile Pro Arg Asn Pro Pro Pro Arg Leu Lys Ser Lys		
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Lys Trp Ser Lys Lys Phe Phe Ser Phe Ile Glu Gly Cys Leu Val Lys		
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Asn Tyr Met Gln Arg Pro Ser Thr Glu Gln Leu Leu Lys His Pro Phe		
	275	280 285
Ile Arg Asp Gln Pro Asn Glu Arg Gln Val Arg Ile Gln Leu Lys Asp		
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His Ile Asp Arg Thr Arg Lys Lys Arg Gly Glu Lys Asp Glu Thr Glu		
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Tyr Glu Tyr Ser Gly Ser Glu Glu Glu Glu Glu Glu Val Pro Glu Gln		
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 580 585 590  
 Glu Pro Pro Val Pro Ser Arg Ser Glu Ser Phe Ser Asn Gly Asn Ser  
 595 600 605  
 Glu Ser Val His Pro Ala Leu Gln Arg Pro Ala Glu Pro Gln Val Pro  
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 Val Arg Thr Thr Ser Arg Ser Pro Val Leu Ser Arg Arg Asp Ser Pro

19

625		630		635		640
Leu Gln Gly Ser	Gly Gln Gln Asn Ser	Gln Ala Gly Gln Arg	Asn Ser			
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Thr Ser Ile Glu	Pro Arg Leu Leu Trp	Glu Arg Val Glu	Lys Leu Val			
	660		665		670	
Pro Arg Pro Gly	Ser Gly Ser Ser	Ser Gly Ser Ser	Asn Ser Gly Ser			
	675		680		685	
Gln Pro Gly Ser	His Pro Gly Ser	Gln Ser Gly Ser	Gly Glu Arg Phe			
	690		700			
Arg Val Arg Ser	Ser Ser Lys Ser	Glu Gly Ser Pro	Ser Gln Arg Leu			
705		710	715		720	
Glu Asn Ala Val	Lys Lys Pro Glu	Asp Lys Lys Glu	Val Phe Arg Pro			
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Leu Lys Pro Ala	Asp Leu Thr Ala	Leu Ala Lys Glu	Leu Arg Ala Val			
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Glu Asp Val Arg	Pro Pro His Lys	Val Thr Asp Tyr	Ser Ser Ser Ser			
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Glu Glu Ser Gly	Thr Thr Asp Glu	Glu Asp Asp Asp	Val Glu Gln Glu			
	770		775		780	
Gly Ala Asp Glu	Ser Thr Ser Gly	Pro Glu Asp Thr	Arg Ala Ala Ser			
785		790	795		800	
Ser Leu Asn Leu	Ser Asn Gly Glu	Thr Glu Ser Val	Lys Thr Met Ile			
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Val His Asp Asp	Val Glu Ser Glu	Pro Ala Met Thr	Pro Ser Lys Glu			
	820		825		830	
Gly Thr Leu Ile	Val Arg Arg Thr	Gln Ser Ala Ser	Ser Thr Leu Gln			
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Lys His Lys Ser	Ser Ser Ser Phe	Thr Pro Phe Ile	Asp Pro Arg Leu			
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Leu Gln Ile Ser	Pro Ser Ser Gly	Thr Thr Val Thr	Ser Val Val Gly			
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Phe Ser Cys Asp	Gly Met Arg Pro	Glu Ala Ile Arg	Gln Asp Pro Thr			
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Arg Lys Gly Ser	Val Val Asn Val	Asn Pro Thr Asn	Thr Arg Pro Gln			
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Ser Asp Thr Pro	Glu Ile Arg Lys	Tyr Lys Lys Arg	Phe Asn Ser Glu			
	915		920		925	

Ile Leu Cys Ala Ala Leu Trp Gly Val Asn Leu Leu Val Gly Thr Glu  
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 Ser Gly Leu Met Leu Leu Asp Arg Ser Gly Gln Gly Lys Val Tyr Pro  
 945 950 955 960  
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 Tyr Leu Ser Trp Leu Arg Asn Lys Ile Leu His Asn Asp Pro Glu Val  
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 1010 1015 1020  
 His Tyr Lys Val Val Lys Tyr Glu Arg Ile Lys Phe Leu Val Ile Ala  
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 Lys Phe Met Ala Phe Lys Ser Phe Gly Glu Leu Val His Lys Pro Leu  
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 1090 1095 1100  
 Tyr Asp Ile Tyr Leu Pro Thr His Ile Gln Cys Ser Ile Lys Pro His  
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 Ala Ile Ile Ile Leu Pro Asn Thr Asp Gly Met Glu Leu Leu Val Cys  
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 Tyr Glu Asp Glu Gly Val Tyr Val Asn Thr Tyr Gly Arg Ile Thr Lys  
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 Arg Ser Asn Gln Thr Met Gly Trp Gly Glu Lys Ala Ile Glu Ile Arg  
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 Ser Val Glu Thr Gly His Leu Asp Gly Val Phe Met His Lys Arg Ala  
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 Gln Arg Leu Lys Phe Leu Cys Glu Arg Asn Asp Lys Val Phe Phe Ala  
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21

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Arg Thr Ser Leu Leu Ser Trp  
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Ala Thr Tyr Tyr Gly Ala Phe Ile Lys Lys Asn Pro Pro Gly Met Asp  
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Asp Gln Leu Trp Leu Val Met Glu Phe Cys Gly Ala Gly Ser Val Thr  
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Asp Leu Ile Lys Asn Thr Lys Gly Asn Thr Leu Lys Glu Glu Trp Ile  
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His Lys Val Ile His Arg Asp Ile Lys Gly Gln Asn Val Leu Leu Thr  
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Glu Asn Ala Glu Val Lys Leu Val Asp Phe Gly Val Ser Ala Gln Leu  
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Asp Arg Thr Val Gly Arg Arg Asn Thr Phe Ile Gly Thr Pro Tyr Trp  
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Met Ala Pro Glu Val Ile Ala Cys Asp Glu Asn Pro Asp Ala Thr Tyr  
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Asp Phe Lys Ser Asp Leu Trp Ser Leu Gly Ile Thr Ala Ile Glu Met  
 180 185 190

Ala Glu Gly Ala Pro Pro Leu Cys Asp Met His Pro Met Arg Ala Leu  
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Phe Leu Ile Pro Arg Asn Pro Ala Pro Arg Leu Lys Ser Lys Lys Trp

22

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Tyr Ser Gly Ser Glu Glu Glu Glu Glu Asn Asp Ser Gly Glu Pro		
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Leu Arg Leu Gln Leu Ala Asn Lys Glu Arg Ser Glu Ala Leu Arg Arg		
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Gln Gln Leu Glu Gln Gln Gln Arg Glu Asn Glu Glu His Lys Arg Gln		
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Leu Leu Ala Glu Arg Gln Lys Arg Ile Glu Glu Gln Lys Glu Gln Arg		
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Arg Arg Leu Glu Glu Gln Gln Arg Arg Glu Lys Glu Leu Arg Lys Gln		
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Gln Glu Arg Glu Gln Arg Arg His Tyr Glu Glu Gln Met Arg Arg Glu		
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Leu Glu Glu Gln Arg Gln Ala Glu Arg Leu Gln Arg Gln Leu Lys Gln		
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Glu Arg Asp Tyr Leu Val Ser Leu Gln His Gln Arg Gln Glu Gln Arg		
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Pro Val Glu Lys Lys Pro Leu Tyr His Tyr Lys Glu Gly Met Ser Pro		
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Ser Glu Lys Pro Ala Trp Ala Lys Glu Val Glu Glu Arg Ser Arg Leu		
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Ser Asp Pro Asn Leu Pro Pro Arg Ser Glu Ser Phe Ser Ile Ser Gly		
	500	505 510

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 580 585 590  
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 Ser Pro Gly Asn Gly Ser Ala Leu Gly Pro Arg Leu Gly Ser Gln Pro  
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 Ile Arg Ala Ser Asn Pro Asp Leu Arg Arg Thr Glu Pro Ile Leu Glu  
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 Ser Pro Leu Gln Arg Thr Ser Ser Gly Ser Ser Ser Ser Ser Ser Thr  
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 Pro Ser Ser Gln Pro Ser Ser Gln Gly Gly Ser Gln Pro Gly Ser Gln  
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 Ala Gly Ser Ser Glu Arg Thr Arg Val Arg Ala Asn Ser Lys Ser Glu  
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 Gly Ser Pro Val Leu Pro His Glu Pro Ala Lys Val Lys Pro Glu Glu  
 705 710 715 720  
 Ser Arg Asp Ile Thr Arg Pro Ser Arg Pro Ala Ser Tyr Lys Lys Ala  
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 Ile Asp Glu Asp Leu Thr Ala Leu Ala Lys Glu Leu Arg Glu Leu Arg  
 740 745 750  
 Ile Glu Glu Thr Asn Arg Pro Met Lys Lys Val Thr Asp Tyr Ser Ser  
 755 760 765  
 Ser Ser Glu Glu Ser Glu Ser Ser Glu Glu Glu Glu Asp Gly Glu  
 770 775 780  
 Ser Glu Thr His Asp Gly Thr Val Ala Val Ser Asp Ile Pro Arg Leu  
 785 790 795 800

Ile Pro Thr Gly Ala Pro Gly Ser Asn Glu Gln Tyr Asn Val Gly Met  
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 Val Gly Thr His Gly Leu Glu Thr Ser His Ala Asp Ser Phe Ser Gly  
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 Ser Ile Ser Arg Glu Gly Thr Leu Met Ile Arg Glu Thr Ser Gly Glu  
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 Asn Leu Pro Asp Leu Val Gln Gln Ser His Ser Pro Ala Gly Thr Pro  
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 Ser Gly Lys Lys Asn Lys Leu Arg Val Tyr Tyr Leu Ser Trp Leu Arg  
                             1045                            1050                            1055  
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 Ile Thr Val Gly Asp Leu Glu Gly Cys Ile His Tyr Lys Val Val Lys  
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25

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Glu Glu Gly Gln Arg Leu Lys Val	Ile Phe Gly Ser His Thr Gly Phe	
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His Val Ile Asp Val Asp Ser Gly Asn Ser Tyr Asp	Ile Tyr Thr Pro	
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Ser His Ile Gln Gly Asn Ile Thr Pro His Ala	Ile Val Ile Leu Pro	
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Lys Thr Asp Gly Met Glu Met Leu Val Cys Tyr Glu Asp Glu Gly Val		
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Tyr Val Asn Thr Tyr Gly Arg Ile Thr Lys Asp Val Val Leu Gln Trp		
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Gly Glu Met Pro Thr Ser Val Ala Tyr Ile His Ser Asn Gln Ile Met		
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Gly Trp Gly Glu Lys Ala Ile Glu Ile Arg Ser Val Glu Thr Gly His		
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Leu Asp Gly Val Phe Met His Lys Arg Ala Gln Arg Leu Lys Phe Leu		
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Cys Glu Arg Asn Asp Lys Val Phe Phe Ala Ser Val Arg Ser Gly Gly		
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Trp

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 <213> Mammalian (Human) ZC3

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26

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 Asp Gln Leu Trp Leu Val Met Glu Phe Cys Gly Ala Gly Ser Val Thr  
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 Asp Leu Val Lys Asn Thr Lys Gly Asn Ala Leu Lys Glu Asp Cys Ile  
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 Ala Tyr Ile Cys Arg Glu Ile Leu Arg Gly Leu Ala His Leu His Ala  
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 His Lys Val Ile His Arg Asp Ile Lys Gly Gln Asn Val Leu Leu Thr  
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 165 170 175  
 Asp Tyr Arg Ser Asp Ile Trp Ser Leu Gly Ile Thr Ala Ile Glu Met  
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 Ala Glu Gly Ala Pro Pro Leu Cys Asp Met His Pro Met Arg Ala Leu  
 195 200 205  
 Phe Leu Ile Pro Arg Asn Pro Pro Pro Arg Leu Lys Ser Lys Lys Trp  
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 Ser Lys Lys Phe Ile Asp Phe Ile Asp Thr Cys Leu Ile Lys Thr Tyr  
 225 230 235 240  
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 Asp Gln Pro Thr Glu Arg Gln Val Arg Ile Gln Leu Lys Asp His Ile  
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 Tyr Ser Gly Ser Glu Glu Glu Asp Asp Ser His Gly Glu Glu Gly Glu  
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 Pro Ser Ser Ile Met Asn Val Pro Gly Glu Ser Thr Leu Arg Arg Glu  
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 Phe Leu Arg Leu Gln Gln Glu Asn Lys Ser Asn Ser Glu Ala Leu Lys  
 325 330 335

Gln Gln Gln Gln Leu Gln Gln Gln Gln Gln Arg Asp Pro Glu Ala His  
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 Ile Lys His Leu Leu His Gln Arg Gln Arg Arg Ile Glu Glu Gln Lys  
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 Glu Glu Arg Arg Arg Val Glu Glu Gln Gln Arg Arg Glu Arg Glu Gln  
 370 375 380  
 Arg Lys Leu Gln Glu Lys Glu Gln Gln Arg Arg Leu Glu Asp Met Gln  
 385 390 395 400  
 Ala Leu Arg Arg Glu Glu Glu Arg Arg Gln Ala Glu Arg Glu Gln Glu  
 405 410 415  
 Tyr Ile Arg His Arg Leu Glu Glu Glu Gln Arg Gln Leu Glu Ile Leu  
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 Lys Gln Leu Glu Glu Gln Arg Gln Ser Glu Arg Leu Gln Arg Gln Leu  
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 Gln Gln Glu His Ala Tyr Leu Lys Ser Leu Gln Gln Gln Gln Gln Gln  
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 Pro Ile Pro Gln Ala Ser Pro Gly Pro Pro Gly Pro Leu Ser Gln Thr  
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 Pro Pro Met Gln Arg Pro Val Glu Pro Gln Glu Gly Pro His Lys Ser  
 565 570 575  
 Leu Val Ala His Arg Val Pro Leu Lys Pro Tyr Ala Ala Pro Val Pro  
 580 585 590  
 Arg Ser Gln Ser Leu Gln Asp Gln Pro Thr Arg Asn Leu Ala Ala Phe  
 595 600 605  
 Pro Ala Ser His Asp Pro Asp Pro Ala Ile Pro Ala Pro Thr Ala Thr  
 610 615 620

Pro Ser Ala Arg Gly Ala Val Ile Arg Gln Asn Ser Asp Pro Thr Ser  
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 Glu Gly Pro Gly Pro Ser Pro Asn Pro Pro Ala Trp Val Arg Pro Asp  
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 Pro Gly Trp Glu Arg Ser Asp Ser Val Leu Pro Ala Ser His Gly His  
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 Leu Pro Gln Ala Gly Ser Leu Glu Arg Asn Arg Val Gly Val Ser Ser  
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 Lys Pro Asp Ser Ser Pro Val Leu Ser Pro Gly Asn Lys Ala Lys Pro  
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 Lys Glu Arg Thr Leu Asp Glu Ala Pro Arg Pro Pro Lys Lys Ala Met  
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 Glu Glu Gly Glu Gly Gly Pro Ala Glu Gly Ser Arg Asp Thr Pro Gly  
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 Gly Arg Asp Gly Asp Thr Asp Ser Val Ser Thr Met Val Val His Asp  
 850 855 860  
 Val Glu Glu Ile Thr Gly Thr Gln Pro Pro Tyr Gly Gly Gly Thr Met  
 865 870 875 880  
 Val Val Gln Arg Thr Pro Glu Glu Glu Arg Asn Leu Leu His Ala Asp  
 885 890 895  
 Ser Asn Gly Tyr Thr Asn Leu Pro Asp Val Val Gln Pro Ser His Ser  
 900 905 910  
 Pro Thr Glu Asn Ser Lys Gly Gln Ser Pro Pro Ser Lys Asp Gly Ser



915	920	925
Gly Asp Tyr Gln Ser Arg	Gly Leu Val Lys Ala	Pro Gly Lys Ser Ser
930	935	940
Phe Thr Met Phe Val Asp	Leu Gly Ile Tyr Gln	Pro Gly Gly Ser Gly
945	950	955
Asp Ser Ile Pro Ile Thr	Ala Leu Val Gly Gly	Glu Gly Thr Arg Leu
965	970	975
Asp Gln Leu Gln Tyr Asp	Val Arg Lys Gly Ser	Val Val Asn Val Asn
980	985	990
Pro Thr Asn Thr Arg Ala	His Ser Glu Thr Pro	Glu Ile Arg Lys Tyr
995	1000	1005
Lys Lys Arg Phe Asn Ser	Glu Ile Leu Cys Ala	Ala Leu Trp Gly Val
1010	1015	1020
Asn Leu Leu Val Gly Thr	Glu Asn Gly Leu Met	Leu Leu Asp Arg Ser
1025	1030	1035
Gly Gln Gly Lys Val Tyr	Gly Leu Ile Gly Arg	Arg Arg Phe Gln Gln
1045	1050	1055
Met Asp Val Leu Glu Gly	Leu Asn Leu Leu Ile	Thr Ile Ser Gly Lys
1060	1065	1070
Arg Asn Lys Leu Arg Val	Tyr Tyr Leu Ser Trp	Leu Arg Asn Lys Ile
1075	1080	1085
Leu His Asn Asp Pro Glu	Val Glu Lys Lys Gln	Gly Trp Thr Thr Val
1090	1095	1100
Gly Asp Met Glu Gly Cys	Gly His Tyr Arg Val	Val Lys Tyr Glu Arg
1105	1110	1115
Ile Lys Phe Leu Val Ile	Ala Leu Lys Ser Ser	Val Glu Val Tyr Ala
1125	1130	1135
Trp Ala Pro Lys Pro Tyr	His Lys Phe Met Ala	Phe Lys Ser Phe Ala
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Asp Leu Pro His Arg Pro	Leu Leu Val Asp Leu	Thr Val Glu Glu Gly
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Gln Arg Leu Lys Val Ile	Tyr Gly Ser Ser Ala	Gly Phe His Ala Val
1170	1175	1180
Asp Val Asp Ser Gly Asn	Ser Tyr Asp Ile Tyr	Ile Pro Val His Ile
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Gln Ser Gln Ile Thr Pro	His Ala Ile Ile Phe	Leu Pro Asn Thr Asp

30

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Gly Met Glu Met Leu Leu Cys Tyr Glu Asp Glu Gly Val Tyr Val Asn	1220		1225		1230
Thr Tyr Gly Arg Ile Ile Lys Asp Val Val Leu Gln Trp Gly Glu Met	1235		1240		1245
Pro Thr Ser Val Ala Tyr Ile Cys Ser Asn Gln Ile Met Gly Trp Gly	1250		1255		1260
Glu Lys Ala Ile Glu Ile Arg Ser Val Glu Thr Gly His Leu Asp Gly	1265		1270		1275
Val Phe Met His Lys Arg Ala Gln Arg Leu Lys Phe Leu Cys Glu Arg	1285		1290		1295
Asn Asp Lys Val Phe Phe Ala Ser Val Arg Ser Gly Gly Ser Ser Gln	1300		1305		1310
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Trp Gly Val Asn Leu Leu Leu Gly Thr Arg Ser Asn Leu Tyr Leu Met	35	40	45	
Asp Arg Ser Gly Lys Ala Asp Ile Thr Lys Leu Ile Arg Arg Arg Pro	50	55	60	
Phe Arg Gln Ile Gln Val Leu Glu Pro Leu Asn Leu Leu Ile Thr Ile	65	70	75	80
Ser Gly His Lys Asn Arg Leu Arg Val Tyr His Leu Thr Trp Leu Arg	85	90	95	
Asn Lys Ile Leu Asn Asn Asp Pro Glu Ser Lys Arg Arg Gln Glu Glu	100	105	110	
Met Leu Lys Thr Glu Glu Ala Cys Lys Ala Ile Asp Lys Leu Thr Gly	115	120	125	

31

Cys Glu His Phe Ser Val Leu Gln His Glu Glu Thr Thr Tyr Ile Ala  
 130 135 140  
 Ile Ala Leu Lys Ser Ser Ile His Leu Tyr Ala Trp Ala Pro Lys Ser  
 145 150 155 160  
 Phe Asp Glu Ser Thr Ala Ile Lys Val Phe Pro Thr Leu Asp His Lys  
 165 170 175  
 Pro Val Thr Val Asp Leu Ala Ile Gly Ser Glu Lys Arg Leu Lys Ile  
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 Val Met Ser Asp Val Thr Leu Pro Lys Asn Pro Leu Glu Ile Ile Ile  
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 Pro Gln Asn Ile Ile Ile Leu Pro Asp Cys Leu Gly Ile Gly Met Met  
 225 230 235 240  
 Leu Thr Phe Asn Ala Glu Ala Leu Ser Val Glu Ala Asn Glu Gln Leu  
 245 250 255  
 Phe Lys Lys Ile Leu Glu Met Trp Lys Asp Ile Pro Ser Ser Ile Ala  
 260 265 270  
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 275 280 285  
 Val Arg Ser Leu Gln Ser Arg Val Leu Glu Ser Glu Leu Lys Arg Arg  
 290 295 300  
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<210> 17  
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<400> 17

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33

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&lt;210&gt; 18

&lt;211&gt; 894

&lt;212&gt; PRT

&lt;213&gt; Mammalian (Human) KHS2

&lt;400&gt; 18

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      35             40             45

Leu Glu Pro Gly Glu Asp Phe Ala Val Val Gln Gln Glu Ile Ile Met
      50             55             60

Met Lys Asp Cys Lys His Pro Asn Ile Val Ala Tyr Phe Gly Ser Tyr
      65             70             75             80

Leu Arg Arg Asp Lys Leu Trp Ile Cys Met Glu Phe Cys Gly Gly Gly
      85             90             95

Ser Leu Gln Asp Ile Tyr His Val Thr Gly Pro Leu Ser Glu Leu Gln
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Ile Ala Tyr Val Ser Arg Glu Thr Leu Gln Gly Leu Tyr Tyr Leu His
      115            120            125

Ser Lys Gly Lys Met His Arg Asp Ile Lys Gly Ala Asn Ile Leu Leu
      130            135            140

Thr Asp Asn Gly His Val Lys Leu Ala Asp Phe Gly Val Ser Ala Gln
      145            150            155            160

Ile Thr Ala Thr Ile Ala Lys Arg Lys Ser Phe Ile Gly Thr Pro Tyr
      165            170            175

Trp Met Ala Pro Glu Val Ala Ala Val Glu Arg Lys Gly Gly Tyr Asn
      180            185            190

Gln Leu Cys Asp Leu Trp Ala Val Gly Ile Thr Ala Ile Glu Leu Ala
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35

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Glu Thr Ser Met Glu Gln Leu Phe Pro Arg Arg Cys Thr Trp Leu Tyr 595	600	605
Val Met Asn Asn Cys Leu Leu Ser Ile Ser Gly Lys Ala Ser Gln Leu 610	615	620
Tyr Ser His Asn Leu Pro Gly Leu Phe Asp Tyr Ala Arg Gln Met Gln 625	630	635
Lys Leu Pro Val Ala Ile Pro Ala His Lys Leu Pro Asp Arg Ile Leu 645	650	655
Pro Arg Lys Phe Ser Val Ser Ala Lys Ile Pro Glu Thr Lys Trp Cys 660	665	670
Gln Lys Cys Cys Val Val Arg Asn Pro Tyr Thr Gly His Lys Tyr Leu 675	680	685
Cys Gly Ala Leu Gln Thr Ser Ile Val Leu Leu Glu Trp Val Glu Pro 690	695	700
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ctaaccagct	agagtacaat	aagagaaggg	aacgggaact	gaggcgaaaa	catgtcatgg	2100
aagttcgaca	acaaccttaag	agtctgaagt	ctaaagaact	ccaaataaaa	aagcagtttc	2160
aggatacctg	caaaattcaa	accagacagt	acaaagcatt	aaggaatcac	ctactggaga	2220
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&lt;210&gt; 22

&lt;211&gt; 898

40

&lt;212&gt; PRT

&lt;213&gt; Mammalian (Human) SULU1

&lt;400&gt; 22

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Met Arg Lys Gly Val Leu Lys Asp Pro Glu Ile Asp Asp Leu Phe Tyr
 1              5              10              15

Lys Asp Asp Pro Glu Glu Leu Phe Ile Gly Leu His Glu Ile Gly His
      20              25              30

Gly Ser Phe Gly Ala Val Tyr Phe Ala Thr Asn Ala His Thr Asn Glu
      35              40              45

Val Val Ala Ile Lys Lys Met Ser Tyr Ser Gly Lys Gln Thr His Glu
 50              55              60

Lys Trp Gln Asp Ile Leu Lys Glu Val Lys Phe Leu Arg Gln Leu Lys
65              70              75              80

His Pro Asn Thr Ile Glu Tyr Lys Gly Cys Tyr Leu Lys Glu His Thr
      85              90              95

Ala Trp Leu Val Met Glu Tyr Cys Leu Gly Ser Ala Ser Asp Leu Leu
      100              105              110

Glu Val His Lys Lys Pro Leu Gln Glu Val Glu Ile Ala Ala Ile Thr
      115              120              125

His Gly Ala Leu His Gly Leu Ala Tyr Leu His Ser His Ala Leu Ile
      130              135              140

His Arg Asp Ile Lys Ala Gly Asn Ile Leu Leu Thr Glu Pro Gly Gln
      145              150              155              160

Val Lys Leu Ala Asp Phe Gly Ser Ala Ser Met Ala Ser Pro Ala Asn
      165              170              175

Ser Phe Val Gly Thr Pro Tyr Trp Met Ala Pro Glu Val Ile Leu Ala
      180              185              190

Met Asp Glu Gly Gln Tyr Asp Gly Lys Val Asp Ile Trp Ser Leu Gly
      195              200              205

Ile Thr Cys Ile Glu Leu Ala Glu Arg Lys Pro Pro Leu Phe Asn Met
      210              215              220

Asn Ala Met Ser Ala Leu Tyr His Ile Ala Gln Asn Asp Ser Pro Thr
      225              230              235              240

Leu Gln Ser Asn Glu Trp Thr Asp Ser Phe Arg Arg Phe Val Asp Tyr
      245              250              255

Cys Leu Gln Lys Ile Pro Gln Glu Arg Pro Thr Ser Ala Glu Leu Leu
      260              265              270

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41

Arg His Asp Phe Val Arg Arg Asp Arg Pro Leu Arg Val Leu Ile Asp  
 275 280 285  
 Leu Ile Gln Arg Thr Lys Asp Ala Val Arg Glu Leu Asp Asn Leu Gln  
 290 295 300  
 Tyr Arg Lys Met Lys Lys Ile Leu Phe Gln Glu Thr Arg Asn Gly Pro  
 305 310 315 320  
 Leu Asn Glu Ser Gln Glu Asp Glu Glu Asp Ser Glu His Gly Thr Ser  
 325 330 335  
 Leu Asn Arg Glu Met Asp Ser Leu Gly Ser Asn His Ser Ile Pro Ser  
 340 345 350  
 Met Ser Val Ser Thr Gly Ser Gln Ser Ser Ser Val Asn Ser Met Gln  
 355 360 365  
 Glu Val Met Asp Glu Ser Ser Ser Glu Leu Val Met Met His Asp Asp  
 370 375 380  
 Glu Ser Thr Ile Asn Ser Ser Ser Ser Val Val His Lys Lys Asp His  
 385 390 395 400  
 Val Phe Thr Arg Asp Glu Ala Gly His Gly Asp Pro Arg Pro Glu Pro  
 405 410 415  
 Arg Pro Thr Gln Ser Val Gln Ser Gln Ala Leu His Tyr Arg Asn Arg  
 420 425 430  
 Glu Arg Phe Ala Thr Ile Lys Ser Ala Ser Leu Val Thr Arg Gln Ile  
 435 440 445  
 His Glu His Glu Gln Glu Asn Glu Leu Arg Glu Gln Met Ser Gly Tyr  
 450 455 460  
 Lys Arg Met Arg Arg Gln His Gln Lys Gln Leu Ile Ala Leu Glu Asn  
 465 470 475 480  
 Lys Leu Lys Ala Glu Met Asp Glu His Arg Leu Lys Leu Gln Lys Glu  
 485 490 495  
 Val Glu Thr His Ala Asn Asn Ser Ser Ile Glu Leu Glu Lys Leu Ala  
 500 505 510  
 Lys Lys Gln Val Ala Ile Ile Glu Lys Glu Ala Lys Val Ala Ala Ala  
 515 520 525  
 Asp Glu Lys Lys Phe Gln Gln Gln Ile Leu Ala Gln Gln Lys Lys Asp  
 530 535 540  
 Leu Thr Thr Phe Leu Glu Ser Gln Lys Lys Gln Tyr Lys Ile Cys Lys  
 545 550 555 560  
 Glu Lys Ile Lys Glu Glu Met Asn Glu Asp His Ser Thr Pro Lys Lys

42

	565		570		575	
Glu Lys Gln	Glu Arg Ile Ser Lys	His Lys Glu Asn Leu	Gln His Thr			
	580	585	590			
Gln Ala Glu	Glu Glu Ala His Leu	Leu Thr Gln Gln Arg	Leu Tyr Tyr			
	595	600	605			
Asp Lys Asn	Cys Arg Phe Phe Lys	Arg Lys Ile Met	Ile Lys Arg His			
	610	615	620			
Glu Val Glu	Gln Gln Asn Ile Arg	Glu Glu Leu Asn	Lys Lys Arg Thr			
	625	630	635	640		
Gln Lys Glu	Met Glu His Ala Met	Leu Ile Arg His	Asp Glu Ser Thr			
	645	650	655			
Arg Glu Leu	Glu Tyr Arg Gln Leu	His Thr Leu Gln	Lys Leu Arg Met			
	660	665	670			
Asp Leu Ile	Arg Leu Gln His Gln	Thr Glu Leu Glu	Asn Gln Leu Glu			
	675	680	685			
Tyr Asn Lys	Arg Arg Glu Arg Glu	Leu His Arg Lys	His Val Met Gly			
	690	695	700			
Leu Arg Gln	Gln Pro Lys Asn Leu	Lys Ala Met Glu	Met Gln Ile Lys			
	705	710	715	720		
Lys Gln Phe	Gln Asp Thr Cys Lys	Val Gln Thr Lys	Gln Tyr Lys Ala			
	725	730	735			
Leu Lys Asn	His Gln Leu Glu Val	Thr Pro Lys Asn	Glu His Lys Thr			
	740	745	750			
Ile Leu Lys	Thr Leu Lys Asp Glu	Gln Thr Arg Lys	Leu Ala Ile Leu			
	755	760	765			
Ala Glu Gln	Tyr Glu Gln Ser Ile	Asn Glu Met Met	Ala Ser Gln Ala			
	770	775	780			
Leu Arg Leu	Asp Glu Ala Gln Glu	Ala Glu Cys Gln	Ala Leu Arg Leu			
	785	790	795	800		
Gln Leu Gln	Gln Glu Met Glu Leu	Leu Asn Ala Tyr	Gln Ser Lys Ile			
	805	810	815			
Lys Met Gln	Thr Glu Ala Gln His	Glu Arg Glu Leu	Gln Lys Leu Glu			
	820	825	830			
Gln Arg Val	Ser Leu Arg Arg Ala	His Leu Glu Gln	Lys Ile Glu Glu			
	835	840	845			
Glu Leu Ala	Ala Leu Gln Lys Glu	Arg Ser Glu Arg	Ile Lys Asn Leu			
	850	855	860			

43

Leu Glu Arg Gln Glu Arg Glu Ile Glu Thr Phe Asp Met Glu Ser Leu  
 865 870 875 880

Arg Met Gly Phe Gly Asn Leu Val Thr Leu Asp Phe Pro Lys Glu Asp  
 885 890 895

Tyr Arg

<210> 23  
 <211> 786  
 <212> PRT  
 <213> Mammalian (Human) SULU3

<400> 23

Ile Glu Leu Ala Glu Arg Lys Pro Pro Leu Phe Asn Met Asn Ala Met  
 1 5 10 15

Ser Ala Leu Tyr His Ile Ala Gln Asn Glu Ser Pro Thr Leu Gln Ser  
 20 25 30

Asn Glu Trp Ser Asp Tyr Phe Arg Asn Phe Val Asp Ser Cys Leu Gln  
 35 40 45

Lys Ile Pro Gln Asp Arg Pro Thr Ser Glu Glu Leu Leu Lys His Ile  
 50 55 60

Phe Val Leu Arg Glu Arg Pro Glu Thr Val Leu Ile Asp Leu Ile Gln  
 65 70 75 80

Arg Thr Lys Asp Ala Val Arg Glu Leu Asp Asn Leu Gln Tyr Arg Lys  
 85 90 95

Met Lys Lys Leu Leu Phe Gln Glu Ala His Asn Gly Pro Ala Val Glu  
 100 105 110

Ala Gln Glu Glu Glu Glu Gln Asp His Gly Val Gly Arg Thr Gly  
 115 120 125

Thr Val Asn Ser Val Gly Ser Asn Gln Ser Ile Pro Ser Met Ser Ile  
 130 135 140

Ser Ala Ser Ser Gln Ser Ser Ser Val Asn Ser Leu Pro Asp Val Ser  
 145 150 155 160

Asp Asp Lys Ser Glu Leu Asp Met Met Glu Gly Asp His Thr Val Met  
 165 170 175

Ser Asn Ser Ser Val Ile His Leu Lys Pro Glu Glu Glu Asn Tyr Arg  
 180 185 190

Glu Glu Gly Asp Pro Arg Thr Arg Ala Ser Asp Pro Gln Ser Pro Pro  
 195 200 205  
 Gln Val Ser Arg His Lys Ser His Tyr Arg Asn Arg Glu His Phe Ala  
 210 215 220  
 Thr Ile Arg Thr Ala Ser Leu Val Thr Arg Gln Met Gln Glu His Glu  
 225 230 235 240  
 Gln Asp Ser Glu Leu Arg Glu Gln Met Ser Gly Tyr Lys Arg Met Arg  
 245 250 255  
 Arg Gln His Gln Lys Gln Leu Met Thr Leu Glu Asn Lys Leu Lys Ala  
 260 265 270  
 Glu Met Asp Glu His Arg Leu Arg Leu Asp Lys Asp Leu Glu Thr Gln  
 275 280 285  
 Arg Asn Asn Phe Ala Ala Glu Met Glu Lys Leu Ile Lys Lys His Gln  
 290 295 300  
 Ala Ala Met Glu Lys Glu Ala Lys Val Met Ser Asn Glu Glu Lys Lys  
 305 310 315 320  
 Phe Gln Gln His Ile Gln Ala Gln Gln Lys Lys Glu Leu Asn Ser Phe  
 325 330 335  
 Leu Glu Ser Gln Lys Arg Glu Tyr Lys Leu Arg Lys Glu Gln Leu Lys  
 340 345 350  
 Glu Glu Leu Asn Glu Asn Gln Ser Thr Pro Lys Lys Glu Lys Gln Glu  
 355 360 365  
 Trp Leu Ser Lys Gln Lys Glu Asn Ile Gln His Phe Gln Ala Glu Glu  
 370 375 380  
 Glu Ala Asn Leu Leu Arg Arg Gln Arg Gln Tyr Leu Glu Leu Glu Cys  
 385 390 395 400  
 Arg Arg Phe Lys Arg Arg Met Leu Leu Gly Arg His Asn Leu Glu Gln  
 405 410 415  
 Asp Leu Val Arg Glu Glu Leu Asn Lys Arg Gln Thr Gln Lys Asp Leu  
 420 425 430  
 Glu His Ala Met Leu Leu Arg Gln His Glu Ser Met Gln Glu Leu Glu  
 435 440 445  
 Phe Arg His Leu Asn Thr Ile Gln Lys Met Arg Cys Glu Leu Ile Arg  
 450 455 460  
 Leu Gln His Gln Thr Glu Leu Thr Asn Gln Leu Glu Tyr Asn Lys Arg  
 465 470 475 480  
 Arg Glu Arg Glu Leu Arg Arg Lys His Val Met Glu Val Arg Gln Gln



45

485

490

495

Pro Lys Ser Leu Lys Ser Lys Glu Leu Gln Ile Lys Lys Gln Phe Gln  
 500 505 510

Asp Thr Cys Lys Ile Gln Thr Arg Gln Tyr Lys Ala Leu Arg Asn His  
 515 520 525

Leu Leu Glu Thr Thr Pro Lys Ser Glu His Lys Ala Val Leu Lys Arg  
 530 535 540

Leu Lys Glu Glu Gln Thr Arg Lys Leu Ala Ile Leu Ala Glu Gln Tyr  
 545 550 555 560

Asp His Ser Ile Asn Glu Met Leu Ser Thr Gln Ala Leu Arg Leu Asp  
 565 570 575

Glu Ala Gln Glu Ala Glu Cys Gln Val Leu Lys Met Gln Leu Gln Gln  
 580 585 590

Glu Leu Glu Leu Leu Asn Ala Tyr Gln Ser Lys Ile Lys Met Gln Ala  
 595 600 605

Glu Ala Gln His Asp Arg Glu Leu Arg Glu Leu Glu Gln Arg Val Ser  
 610 615 620

Leu Arg Arg Ala Leu Leu Glu Gln Lys Ile Glu Glu Glu Met Leu Ala  
 625 630 635 640

Leu Gln Asn Glu Arg Thr Glu Arg Ile Arg Ser Leu Leu Glu Arg Gln  
 645 650 655

Ala Arg Glu Ile Glu Ala Phe Asp Ser Glu Ser Met Arg Leu Gly Phe  
 660 665 670

Ser Asn Met Val Leu Ser Asn Leu Ser Pro Glu Ala Phe Ser His Ser  
 675 680 685

Tyr Pro Gly Ala Ser Gly Trp Ser His Asn Pro Thr Gly Gly Pro Gly  
 690 695 700

Pro His Trp Gly His Pro Met Gly Gly Pro Pro Gln Ala Trp Gly His  
 705 710 715 720

Pro Met Gln Gly Gly Pro Gln Pro Trp Gly His Pro Ser Gly Pro Met  
 725 730 735

Gln Gly Val Pro Arg Gly Ser Ser Met Gly Val Arg Asn Ser Pro Gln  
 740 745 750

Ala Leu Arg Arg Thr Ala Ser Gly Gly Arg Thr Glu Gln Gly Met Ser  
 755 760 765

Arg Ser Thr Ser Val Thr Ser Gln Ile Ser Asn Gly Ser His Met Ser  
 770 775 780

Tyr Thr  
785

<210> 24  
<211> 748  
<212> PRT  
<213> Mammalian (Murine) SULU3

<400> 24

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			20					25					30			
Glu	Ile	Gly	His	Gly	Ser	Phe	Gly	Ala	Val	Tyr	Phe	Ala	Arg	Asp	Val	
		35					40					45				
Arg	Thr	Asn	Glu	Val	Val	Ala	Ile	Lys	Lys	Met	Ser	Tyr	Ser	Gly	Lys	
		50				55					60					
Gln	Ser	Thr	Glu	Lys	Trp	Gln	Asp	Ile	Ile	Lys	Glu	Val	Lys	Phe	Leu	
65					70					75					80	
Gln	Arg	Ile	Lys	His	Pro	Asn	Ser	Ile	Glu	Tyr	Lys	Gly	Cys	Tyr	Leu	
				85				90						95		
Arg	Glu	His	Thr	Ala	Trp	Leu	Val	Met	Glu	Tyr	Cys	Leu	Gly	Ser	Ala	
			100					105					110			
Ser	Asp	Leu	Leu	Glu	Val	His	Lys	Lys	Pro	Leu	Gln	Glu	Val	Glu	Ile	
		115					120					125				
Ala	Ala	Ile	Thr	His	Gly	Ala	Leu	Gln	Gly	Leu	Ala	Tyr	Leu	His	Ser	
		130				135					140					
His	Thr	Met	Ile	His	Arg	Asp	Ile	Lys	Ala	Gly	Asn	Ile	Leu	Leu	Thr	
145					150					155					160	
Glu	Pro	Gly	Gln	Val	Lys	Leu	Ala	Asp	Phe	Gly	Ser	Ala	Ser	Met	Ala	
				165					170					175		
Ser	Pro	Ala	Asn	Ser	Phe	Val	Gly	Thr	Pro	Tyr	Trp	Met	Ala	Pro	Glu	
			180					185					190			
Val	Ile	Leu	Ala	Met	Asp	Glu	Gly	Gln	Tyr	Asp	Gly	Lys	Val	Asp	Val	
		195					200					205				
Trp	Ser	Leu	Gly	Ile	Thr	Cys	Ile	Glu	Leu	Ala	Glu	Arg	Lys	Pro	Pro	
		210				215						220				

Leu Phe Asn Met Asn Ala Met Ser Ala Leu Tyr His Ile Ala Gln Asn  
 225 230 235 240  
 Glu Ser Pro Thr Leu Gln Ser Asn Met Asn Asp Ser Cys Leu Gln Lys  
 245 250 255  
 Ile Pro Gln Asp Arg Pro Thr Ser Glu Glu Leu Leu Lys His Met Phe  
 260 265 270  
 Val Leu Arg Glu Arg Pro Glu Thr Val Leu Ile Asp Leu Ile Gln Arg  
 275 280 285  
 Thr Lys Asp Ala Val Arg Glu Leu Asp Asn Leu Gln Tyr Arg Lys Met  
 290 295 300  
 Lys Lys Leu Leu Phe Gln Glu Ala His Asn Gly Pro Ala Val Glu Ala  
 305 310 315 320  
 Gln Glu Glu Glu Glu Glu Gln Asp His Gly Val Gly Arg Thr Gly Thr  
 325 330 335  
 Val Asn Ser Val Gly Ser Asn Gln Ser Ile Pro Ser Met Ser Ile Ser  
 340 345 350  
 Ala Ser Ser Gln Ser Ser Ser Val Asn Ser Leu Pro Asp Ala Ser Asp  
 355 360 365  
 Asp Lys Ser Glu Leu Asp Met Met Glu Gly Asp His Thr Val Met Ser  
 370 375 380  
 Asn Ser Ser Val Ile His Leu Lys Pro Glu Glu Glu Asn Tyr Gln Glu  
 385 390 395 400  
 Glu Gly Asp Pro Arg Thr Arg Ala Ser Asp Pro Gln Ser Pro Pro Gln  
 405 410 415  
 Val Ser Arg His Lys Ser His Tyr Arg Asn Arg Glu His Phe Ala Thr  
 420 425 430  
 Ile Arg Thr Ala Ser Leu Val Thr Arg Gln Met Gln Glu His Glu Gln  
 435 440 445  
 Asp Ser Glu Leu Arg Glu Gln Met Ser Gly Tyr Lys Arg Met Arg Arg  
 450 455 460  
 Gln His Gln Lys Gln Leu Met Thr Leu Glu Asn Lys Leu Lys Ala Glu  
 465 470 475 480  
 Met Asp Glu His Arg Leu Arg Leu Asp Lys Asp Leu Glu Thr Gln Arg  
 485 490 495  
 Asn Asn Phe Ala Ala Glu Met Glu Lys Leu Ile Lys Lys His Gln Ala  
 500 505 510  
 Ala Met Glu Lys Glu Ala Lys Val Met Ala Asn Glu Glu Lys Lys Phe

48

515                      520                      525  
 Gln Gln His Ile Gln Ala Gln Gln Lys Lys Glu Leu Asn Ser Phe Leu  
 530                      535                      540  
 Glu Ser Gln Lys Arg Glu Tyr Lys Leu Arg Lys Glu Gln Leu Lys Glu  
 545                      550                      555                      560  
 Glu Leu Asn Glu Asn Gln Ser Thr Pro Lys Lys Glu Lys Gln Glu Trp  
 565                      570                      575  
 Leu Ser Lys Gln Lys Glu Asn Ile Gln His Phe Gln Ala Glu Glu Glu  
 580                      585                      590  
 Ala Asn Leu Leu Arg Arg Gln Arg Gln Tyr Leu Glu Leu Glu Cys Arg  
 595                      600                      605  
 Arg Phe Lys Arg Arg Met Leu Leu Gly Arg His Asn Leu Glu Gln Asp  
 610                      615                      620  
 Leu Val Arg Glu Glu Leu Asn Lys Arg Gln Thr Gln Lys Asp Leu Glu  
 625                      630                      635                      640  
 His Ala Met Leu Leu Arg Gln His Glu Ser Met Gln Glu Leu Glu Phe  
 645                      650                      655  
 Arg His Leu Asn Thr Ile Gln Lys Met Arg Cys Glu Leu Ile Arg Leu  
 660                      665                      670  
 Gln His Gln Thr Glu Leu Thr Asn Gln Leu Glu Tyr Asn Lys Arg Arg  
 675                      680                      685  
 Glu Arg Glu Leu Arg Arg Lys His Val Met Glu Val Arg Gln Gln Pro  
 690                      695                      700  
 Lys Ser Leu Lys Ser Lys Glu Leu Gln Ile Lys Lys Gln Phe Gln Asp  
 705                      710                      715                      720  
 Thr Cys Lys Ile Gln Thr Arg Gln Tyr Lys Ala Leu Arg Asn His Leu  
 725                      730                      735  
 Leu Glu Thr Thr Pro Lys Asn Glu His Lys Ala Ile  
 740                      745

<210> 25  
 <211> 2795  
 <212> DNA  
 <213> Mammalian (Human) GEK2  
 <400> 25

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 ggcttttgcc aatttcgcgc gcatcctgcg cctgtctacc ttcgagaaga gaaagtcccg      120

cgaatatgag	cacgtccgcc	gogacctgga	ccccaacgag	gtgtgggaga	tcgtgggcga	180
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gcagctgcag	aatgaaaagt	gccacctcct	ggtagagcac	gaaacccaga	aactgaaggc	2760
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&lt;210&gt; 26

&lt;211&gt; 912

&lt;212&gt; PRT

&lt;213&gt; Mammalian (Human) GEK2

&lt;400&gt; 26

Met Ala Phe Ala Asn Phe Arg Arg Ile Leu Arg Leu Ser Thr Phe Glu

50

1	5	10	15
Lys Arg Lys Ser Arg Glu Tyr Glu His Val Arg Arg Asp Leu Asp Pro	20	25	30
Asn Glu Val Trp Glu Ile Val Gly Glu Leu Gly Asp Gly Ala Phe Gly	35	40	45
Lys Val Tyr Lys Ala Lys Asn Lys Glu Thr Gly Ala Leu Ala Ala Ala	50	55	60
Lys Val Ile Glu Thr Lys Ser Glu Glu Glu Leu Glu Asp Tyr Ile Val	65	70	75
Glu Ile Glu Ile Leu Ala Thr Cys Asp His Pro Tyr Ile Val Lys Leu	85	90	95
Leu Gly Ala Tyr Tyr His Asp Gly Lys Leu Trp Ile Met Ile Glu Phe	100	105	110
Cys Pro Gly Gly Ala Val Asp Ala Ile Met Leu Glu Leu Asp Arg Gly	115	120	125
Leu Thr Glu Pro Gln Ile Gln Val Val Cys Arg Gln Met Leu Glu Ala	130	135	140
Leu Asn Phe Leu His Ser Lys Arg Ile Ile His Arg Asp Leu Lys Ala	145	150	155
Gly Asn Val Leu Met Thr Leu Glu Gly Asp Ile Arg Leu Ala Asp Phe	165	170	175
Gly Val Ser Ala Lys Asn Leu Lys Thr Leu Gln Lys Arg Asp Ser Phe	180	185	190
Ile Gly Thr Pro Tyr Trp Met Ala Pro Glu Val Val Met Cys Glu Thr	195	200	205
Met Lys Asp Thr Pro Tyr Asp Tyr Lys Ala Asp Ile Trp Ser Leu Gly	210	215	220
Ile Thr Leu Ile Glu Met Ala Gln Ile Glu Pro Pro His His Glu Leu	225	230	235
Asn Pro Met Arg Val Leu Leu Lys Ile Ala Lys Ser Asp Pro Pro Thr	245	250	255
Leu Leu Thr Pro Ser Lys Trp Ser Val Glu Phe Arg Asp Phe Leu Lys	260	265	270
Ile Ala Leu Asp Lys Asn Pro Glu Thr Arg Pro Ser Ala Ala Gln Leu	275	280	285
Leu Glu His Pro Phe Val Ser Ser Ile Thr Ser Asn Lys Ala Leu Arg	290	295	300

51

Glu Leu Val Ala Glu Ala Lys Ala Glu Val Met Glu Glu Ile Glu Asp  
 305 310 315 320  
 Gly Arg Asp Glu Gly Glu Glu Glu Asp Ala Val Asp Ala Ala Ser Thr  
 325 330 335  
 Leu Glu Asn His Thr Gln Asn Ser Ser Glu Val Ser Pro Pro Ser Leu  
 340 345 350  
 Asn Ala Asp Lys Pro Leu Glu Glu Ser Pro Ser Thr Pro Leu Ala Pro  
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 370 375 380  
 Asp Arg Ser Leu Gln Thr Thr Ser Pro Pro Val Val Ala Pro Gly Asn  
 385 390 395 400  
 Glu Asn Gly Leu Ala Val Pro Val Pro Leu Arg Lys Ser Arg Pro Val  
 405 410 415  
 Ser Met Asp Ala Arg Ile Gln Val Ala Gln Glu Lys Gln Val Ala Glu  
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 Gln Gly Gly Asp Leu Ser Pro Ala Ala Asn Arg Ser Gln Lys Ala Ser  
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 Gln Ser Arg Pro Asn Ser Ser Ala Leu Glu Thr Leu Gly Gly Glu Lys  
 450 455 460  
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 Ser Lys Arg Asp Ser Asp Cys Ser Ser Leu Cys Thr Ser Glu Ser Met  
 485 490 495  
 Asp Tyr Gly Thr Asn Leu Ser Thr Asp Leu Ser Leu Asn Lys Glu Met  
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 Gln Met His Lys Arg Phe Glu Gln Glu Ile Asn Ala Lys Lys Lys Phe  
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 Glu Lys Met Glu Gln Asp His Ala Val Arg Arg Arg Glu Glu Ala Arg  
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 Arg Ile Arg Leu Glu Gln Asp Arg Asp Tyr Thr Arg Phe Gln Glu Gln  
 645 650 655  
 Leu Lys Leu Met Lys Lys Glu Val Lys Asn Glu Val Glu Lys Leu Pro  
 660 665 670  
 Arg Gln Gln Arg Lys Glu Ser Met Lys Gln Lys Met Glu Glu His Thr  
 675 680 685  
 Gln Lys Lys Gln Leu Leu Asp Arg Asp Phe Val Ala Lys Gln Lys Glu  
 690 695 700  
 Asp Leu Glu Leu Ala Met Lys Arg Leu Thr Thr Asp Asn Arg Arg Glu  
 705 710 715 720  
 Ile Cys Asp Lys Glu Arg Glu Cys Leu Met Lys Lys Gln Glu Leu Leu  
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 Arg Asp Arg Glu Ala Ala Leu Trp Glu Met Glu Glu His Gln Leu Gln  
 740 745 750  
 Glu Arg His Gln Leu Val Lys Gln Gln Leu Lys Asp Gln Tyr Phe Leu  
 755 760 765  
 Gln Arg His Glu Leu Leu Arg Lys His Glu Lys Glu Arg Glu Gln Met  
 770 775 780  
 Gln Arg Tyr Asn Gln Arg Met Ile Glu Gln Leu Lys Val Arg Gln Gln  
 785 790 795 800  
 Gln Glu Lys Ala Arg Leu Pro Lys Ile Gln Arg Ser Glu Gly Lys Thr  
 805 810 815  
 Arg Met Ala Met Tyr Lys Lys Ser Leu His Ile Asn Gly Gly Gly Ser  
 820 825 830  
 Ala Ala Glu Gln Arg Glu Lys Ile Lys Gln Phe Ser Gln Gln Glu Glu  
 835 840 845  
 Lys Arg Gln Lys Ser Glu Arg Leu Gln Gln Gln Gln Lys His Glu Asn  
 850 855 860  
 Gln Met Arg Asp Met Leu Ala Gln Cys Glu Ser Asn Met Ser Glu Leu  
 865 870 875 880  
 Gln Gln Leu Gln Asn Glu Lys Cys His Leu Leu Val Glu His Glu Thr  
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Gln Lys Leu Lys Ala Leu Asp Glu Ser His Asn Gln Asn Leu Lys Glu  
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<210> 27  
 <211> 3604  
 <212> DNA  
 <213> Mammalian (Human) PAK4

<400> 27

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&lt;210&gt; 28

&lt;211&gt; 2050

&lt;212&gt; DNA

&lt;213&gt; Mammalian (Human) PAK5

&lt;400&gt; 28

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55

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aaaaaaaaaa 2050

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<210> 29  
 <211> 681  
 <212> PRT  
 <213> Mammalian (Human) PAK4

<400> 29

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Phe Val Gly Leu Pro Pro Gln Trp Gln Asn Ile Leu Asp Thr Leu Arg
      35             40             45

Arg Pro Lys Pro Val Val Asp Pro Ser Arg Ile Thr Arg Val Gln Leu
      50             55             60

Gln Pro Met Lys Thr Val Val Arg Gly Ser Ala Met Pro Val Asp Gly
      65             70             75             80

Tyr Ile Ser Gly Leu Leu Asn Asp Ile Gln Lys Leu Ser Val Ile Ser
      85             90             95

Ser Asn Thr Leu Arg Gly Arg Ser Pro Thr Ser Arg Arg Arg Ala Gln
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Ser Leu Gly Leu Leu Gly Asp Glu His Trp Ala Thr Asp Pro Asp Met
      115            120            125

Tyr Leu Gln Ser Pro Gln Ser Glu Arg Thr Asp Pro His Gly Leu Tyr
      130            135            140

Leu Ser Cys Asn Gly Gly Thr Pro Ala Gly His Lys Gln Met Pro Trp
      145            150            155            160

Pro Glu Pro Gln Ser Pro Arg Val Leu Pro Asn Gly Leu Ala Ala Lys
      165            170            175

Ala Gln Ser Leu Gly Pro Ala Glu Phe Gln Gly Ala Ser Gln Arg Cys
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Leu Gln Leu Gly Ala Cys Leu Gln Ser Ser Pro Pro Gly Ala Ser Pro
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56

Pro Thr Gly Thr Asn Arg His Gly Met Lys Ala Ala Lys His Gly Ser  
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 Glu Glu Ala Arg Pro Gln Ser Cys Leu Val Gly Ser Ala Thr Gly Arg  
 225 230 235 240  
 Pro Gly Gly Glu Gly Ser Pro Ser Pro Lys Thr Arg Glu Ser Ser Leu  
 245 250 255  
 Lys Arg Arg Leu Phe Arg Ser Met Phe Leu Ser Thr Ala Ala Thr Ala  
 260 265 270  
 Pro Pro Ser Ser Ser Lys Pro Gly Pro Pro Pro Gln Ser Lys Pro Asn  
 275 280 285  
 Ser Ser Phe Arg Pro Pro Gln Lys Asp Asn Pro Pro Ser Leu Val Ala  
 290 295 300  
 Lys Ala Gln Ser Leu Pro Ser Asp Gln Pro Val Gly Thr Phe Ser Pro  
 305 310 315 320  
 Leu Thr Thr Ser Asp Thr Ser Ser Pro Gln Lys Ser Leu Arg Thr Ala  
 325 330 335  
 Pro Ala Thr Gly Gln Leu Pro Gly Arg Ser Ser Pro Ala Gly Ser Pro  
 340 345 350  
 Arg Thr Trp His Ala Gln Ile Ser Thr Ser Asn Leu Tyr Leu Pro Gln  
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 Asp Pro Thr Val Ala Lys Gly Ala Leu Ala Gly Glu Asp Thr Gly Val  
 370 375 380  
 Val Thr His Glu Gln Phe Lys Ala Ala Leu Arg Met Val Val Asp Gln  
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 Gly Asp Pro Arg Leu Leu Leu Asp Ser Tyr Val Lys Ile Gly Glu Gly  
 405 410 415  
 Ser Thr Gly Ile Val Cys Leu Ala Arg Glu Lys His Ser Gly Arg Gln  
 420 425 430  
 Val Ala Val Lys Met Met Asp Leu Arg Lys Gln Gln Arg Arg Glu Leu  
 435 440 445  
 Leu Phe Asn Glu Val Val Ile Met Arg Asp Tyr Gln His Phe Asn Val  
 450 455 460  
 Val Glu Met Tyr Lys Ser Tyr Leu Val Gly Glu Glu Leu Trp Val Leu  
 465 470 475 480  
 Met Glu Phe Leu Gln Gly Gly Ala Leu Thr Asp Ile Val Ser Gln Val  
 485 490 495  
 Arg Leu Asn Glu Glu Gln Ile Ala Thr Val Cys Glu Ala Val Leu Gln  
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Ala Leu Ala Tyr Leu His Ala Gln Gly Val Ile His Arg Asp Ile Lys  
 515 520 525  
 Ser Asp Ser Ile Leu Leu Thr Leu Asp Gly Arg Val Lys Leu Ser Asp  
 530 535 540  
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 545 550 555 560  
 Leu Val Gly Thr Pro Tyr Trp Met Ala Pro Glu Val Ile Ser Arg Ser  
 565 570 575  
 Leu Tyr Ala Thr Glu Val Asp Ile Trp Ser Leu Gly Ile Met Val Ile  
 580 585 590  
 Glu Met Val Asp Gly Glu Pro Pro Tyr Phe Ser Asp Ser Pro Val Gln  
 595 600 605  
 Ala Met Lys Arg Leu Arg Asp Ser Pro Pro Pro Lys Leu Lys Asn Ser  
 610 615 620  
 His Lys Val Ser Pro Val Leu Arg Asp Phe Leu Glu Arg Met Leu Val  
 625 630 635 640  
 Arg Asp Pro Gln Glu Arg Ala Thr Ala Gln Glu Leu Leu Asp His Pro  
 645 650 655  
 Phe Leu Leu Gln Thr Gly Leu Pro Glu Cys Leu Val Pro Leu Ile Gln  
 660 665 670  
 Leu Tyr Arg Lys Gln Thr Ser Thr Cys  
 675 680

<210> 30  
 <211> 398  
 <212> PRT  
 <213> Mammalian (Human) PAK5

<400> 30

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 Asp Val Ala Pro Asn Gly Pro Ser Ala Gly Gly Leu Ala Ile Pro Gln  
 35 40 45  
 Ser Ser Ser Ser Ser Ser Arg Pro Pro Thr Arg Ala Arg Gly Ala Pro  
 50 55 60

58

Ser Pro Gly Val Leu Gly Pro His Ala Ser Glu Pro Gln Leu Ala Pro  
 65 70 75 80  
 Pro Ala Cys Thr Pro Ala Ala Pro Ala Val Pro Gly Pro Pro Gly Pro  
 85 90 95  
 Arg Ser Pro Gln Arg Glu Pro Gln Arg Val Ser His Glu Gln Phe Arg  
 100 105 110  
 Ala Ala Leu Gln Leu Val Val Asp Pro Gly Asp Pro Arg Ser Tyr Leu  
 115 120 125  
 Asp Asn Phe Ile Lys Ile Gly Glu Gly Ser Thr Gly Ile Val Cys Ile  
 130 135 140  
 Ala Thr Val Arg Ser Ser Gly Lys Leu Val Ala Val Lys Lys Met Asp  
 145 150 155 160  
 Leu Arg Lys Gln Gln Arg Arg Glu Leu Leu Phe Asn Glu Val Val Ile  
 165 170 175  
 Met Arg Asp Tyr Gln His Glu Asn Val Val Glu Met Tyr Asn Ser Tyr  
 180 185 190  
 Leu Val Gly Asp Glu Leu Trp Val Val Met Glu Phe Leu Glu Gly Gly  
 195 200 205  
 Ala Leu Thr Asp Ile Val Thr His Thr Arg Met Asn Glu Glu Gln Ile  
 210 215 220  
 Ala Ala Val Cys Leu Ala Val Leu Gln Ala Leu Ser Val Leu His Ala  
 225 230 235 240  
 Gln Gly Val Ile His Arg Asp Ile Lys Ser Asp Ser Ile Leu Leu Thr  
 245 250 255  
 His Asp Gly Arg Val Lys Leu Ser Asp Phe Gly Phe Cys Ala Gln Val  
 260 265 270  
 Ser Lys Glu Val Pro Arg Arg Lys Ser Leu Val Gly Thr Pro Tyr Trp  
 275 280 285  
 Met Ala Pro Glu Leu Ile Ser Arg Leu Pro Tyr Gly Pro Glu Val Asp  
 290 295 300  
 Ile Trp Ser Leu Gly Ile Met Val Ile Glu Met Val Asp Gly Glu Pro  
 305 310 315 320  
 Pro Tyr Phe Asn Glu Pro Pro Leu Lys Ala Met Lys Met Ile Arg Asp  
 325 330 335  
 Asn Leu Pro Pro Arg Leu Lys Asn Leu His Lys Val Ser Pro Ser Leu  
 340 345 350  
 Lys Gly Phe Leu Asp Arg Leu Leu Val Arg Asp Pro Ala Gln Arg Ala  
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Thr Ala Ala Glu Leu Leu Lys His Pro Phe Leu Ala Lys Ala Gly Pro  
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Pro Ala Ser Ile Val Pro Leu Met Arg Gln Asn Arg Thr Arg  
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<210> 31  
 <211> 1001  
 <212> PRT  
 <213> Mammalian (murine/human) SULU3

<400> 31

Met Pro Ser Thr Asn Arg Ala Gly Ser Leu Lys Asp Pro Glu Ile Ala  
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Glu Leu Phe Phe Lys Glu Asp Pro Glu Lys Leu Phe Thr Asp Leu Arg  
 20 25 30

Glu Ile Gly His Gly Ser Phe Gly Ala Val Tyr Phe Ala Arg Asp Val  
 35 40 45

Arg Thr Asn Glu Val Val Ala Ile Lys Lys Met Ser Tyr Ser Gly Lys  
 50 55 60

Gln Ser Thr Glu Lys Trp Gln Asp Ile Ile Lys Glu Val Lys Phe Leu  
 65 70 75 80

Gln Arg Ile Lys His Pro Asn Ser Ile Glu Tyr Lys Gly Cys Tyr Leu  
 85 90 95

Arg Glu His Thr Ala Trp Leu Val Met Glu Tyr Cys Leu Gly Ser Ala  
 100 105 110

Ser Asp Leu Leu Glu Val His Lys Lys Pro Leu Gln Glu Val Glu Ile  
 115 120 125

Ala Ala Ile Thr His Gly Ala Leu Gln Gly Leu Ala Tyr Leu His Ser  
 130 135 140

His Thr Met Ile His Arg Asp Ile Lys Ala Gly Asn Ile Leu Leu Thr  
 145 150 155 160

Glu Pro Gly Gln Val Lys Leu Ala Asp Phe Gly Ser Ala Ser Met Ala  
 165 170 175

Ser Pro Ala Asn Ser Phe Val Gly Thr Pro Tyr Trp Met Ala Pro Glu  
 180 185 190

Val Ile Leu Ala Met Asp Glu Gly Gln Tyr Asp Gly Lys Val Asp Val  
 195 200 205

Trp Ser Leu Gly Ile Thr Cys Ile Glu Leu Ala Glu Arg Lys Pro Pro

60

210	215	220
Leu Phe Asn Met Asn Ala Met Ser Ala Leu Tyr His Ile Ala Gln Asn		
225	230	235 240
Glu Ser Pro Thr Leu Gln Ser Asn Glu Trp Ser Asp Tyr Phe Arg Asn		
	245	250 255
Phe Val Asp Ser Cys Leu Gln Lys Ile Pro Gln Asp Arg Pro Thr Ser		
	260	265 270
Glu Glu Leu Leu Lys His Ile Phe Val Leu Arg Glu Arg Pro Glu Thr		
	275	280 285
Val Leu Ile Asp Leu Ile Gln Arg Thr Lys Asp Ala Val Arg Glu Leu		
	290	295 300
Asp Asn Leu Gln Tyr Arg Lys Met Lys Lys Leu Leu Phe Gln Glu Ala		
305	310	315 320
His Asn Gly Pro Ala Val Glu Ala Gln Glu Glu Glu Glu Gln Asp		
	325	330 335
His Gly Val Gly Arg Thr Gly Thr Val Asn Ser Val Gly Ser Asn Gln		
	340	345 350
Ser Ile Pro Ser Met Ser Ile Ser Ala Ser Ser Gln Ser Ser Ser Val		
	355	360 365
Asn Ser Leu Pro Asp Val Ser Asp Asp Lys Ser Glu Leu Asp Met Met		
	370	375 380
Glu Gly Asp His Thr Val Met Ser Asn Ser Ser Val Ile His Leu Lys		
385	390	395 400
Pro Glu Glu Glu Asn Tyr Arg Glu Glu Gly Asp Pro Arg Thr Arg Ala		
	405	410 415
Ser Asp Pro Gln Ser Pro Pro Gln Val Ser Arg His Lys Ser His Tyr		
	420	425 430
Arg Asn Arg Glu His Phe Ala Thr Ile Arg Thr Ala Ser Leu Val Thr		
	435	440 445
Arg Gln Met Gln Glu His Glu Gln Asp Ser Glu Leu Arg Glu Gln Met		
	450	455 460
Ser Gly Tyr Lys Arg Met Arg Arg Gln His Gln Lys Gln Leu Met Thr		
465	470	475 480
Leu Glu Asn Lys Leu Lys Ala Glu Met Asp Glu His Arg Leu Arg Leu		
	485	490 495
Asp Lys Asp Leu Glu Thr Gln Arg Asn Asn Phe Ala Ala Glu Met Glu		
	500	505 510



Lys Leu Ile Lys Lys His Gln Ala Ala Met Glu Lys Glu Ala Lys Val  
 515 520 525  
 Met Ser Asn Glu Glu Lys Lys Phe Gln Gln His Ile Gln Ala Gln Gln  
 530 535 540  
 Lys Lys Glu Leu Asn Ser Phe Leu Glu Ser Gln Lys Arg Glu Tyr Lys  
 545 550 555 560  
 Leu Arg Lys Glu Gln Leu Lys Glu Glu Leu Asn Glu Asn Gln Ser Thr  
 565 570 575  
 Pro Lys Lys Glu Lys Gln Glu Trp Leu Ser Lys Gln Lys Glu Asn Ile  
 580 585 590  
 Gln His Phe Gln Ala Glu Glu Glu Ala Asn Leu Leu Arg Arg Gln Arg  
 595 600 605  
 Gln Tyr Leu Glu Leu Glu Cys Arg Arg Phe Lys Arg Arg Met Leu Leu  
 610 615 620  
 Gly Arg His Asn Leu Glu Gln Asp Leu Val Arg Glu Glu Leu Asn Lys  
 625 630 635 640  
 Arg Gln Thr Gln Lys Asp Leu Glu His Ala Met Leu Leu Arg Gln His  
 645 650 655  
 Glu Ser Met Gln Glu Leu Glu Phe Arg His Leu Asn Thr Ile Gln Lys  
 660 665 670  
 Met Arg Cys Glu Leu Ile Arg Leu Gln His Gln Thr Glu Leu Thr Asn  
 675 680 685  
 Gln Leu Glu Tyr Asn Lys Arg Arg Glu Arg Glu Leu Arg Arg Lys His  
 690 695 700  
 Val Met Glu Val Arg Gln Gln Pro Lys Ser Leu Lys Ser Lys Glu Leu  
 705 710 715 720  
 Gln Ile Lys Lys Gln Phe Gln Asp Thr Cys Lys Ile Gln Thr Arg Gln  
 725 730 735  
 Tyr Lys Ala Leu Arg Asn His Leu Leu Glu Thr Thr Pro Lys Ser Glu  
 740 745 750  
 His Lys Ala Val Leu Lys Arg Leu Lys Glu Glu Gln Thr Arg Lys Leu  
 755 760 765  
 Ala Ile Leu Ala Glu Gln Tyr Asp His Ser Ile Asn Glu Met Leu Ser  
 770 775 780  
 Thr Gln Ala Leu Arg Leu Asp Glu Ala Gln Glu Ala Glu Cys Gln Val  
 785 790 795 800  
 Leu Lys Met Gln Leu Gln Gln Glu Leu Glu Leu Leu Asn Ala Tyr Gln

62

	805		810		815
Ser Lys Ile	Lys Met Gln Ala Glu	Ala Gln His Asp Arg	Glu Leu Arg		
	820	825	830		
Glu Leu Glu	Gln Arg Val Ser Leu Arg	Arg Ala Leu Leu Glu	Gln Lys		
	835	840	845		
Ile Glu Glu	Glu Met Leu Ala Leu Gln	Asn Glu Arg Thr	Glu Arg Ile		
	850	855	860		
Arg Ser Leu	Leu Glu Arg Gln Ala Arg	Glu Ile Glu Ala Phe	Asp Ser		
865	870	875	880		
Glu Ser Met	Arg Leu Gly Phe Ser Asn	Met Val Leu Ser Asn	Leu Ser		
	885	890	895		
Pro Glu Ala	Phe Ser His Ser Tyr	Pro Gly Ala Ser Gly	Trp Ser His		
	900	905	910		
Asn Pro Thr	Gly Gly Pro Gly	Pro His Trp Gly	His Pro Met Gly Gly		
	915	920	925		
Pro Pro Gln	Ala Trp Gly His	Pro Met Gln Gly	Gly Pro Gln Pro Trp		
	930	935	940		
Gly His Pro	Ser Gly Pro Met Gln Gly	Val Pro Arg Gly	Ser Ser Met		
945	950	955	960		
Gly Val Arg	Asn Ser Pro Gln Ala Leu Arg	Arg Thr Ala Ser Gly	Gly Gly		
	965	970	975		
Arg Thr Glu	Gln Gly Met Ser Arg Ser	Thr Ser Val Thr Ser	Gln Ile		
	980	985	990		
Ser Asn Gly	Ser His Met Ser Tyr Thr				
	995	1000			

&lt;210&gt; 32

&lt;211&gt; 25

&lt;212&gt; DNA

&lt;213&gt; TRK1

&lt;220&gt;

&lt;223&gt; "n" stands for a, c, g or t.

"y" stands for c or t.

"r" stands for a or g.

&lt;400&gt; 32

ctgaattcgg ngcnttyggg aargt

63

<210> 33  
<211> 24  
<212> DNA  
<213> TRK4

<220>  
<223> "n" stands for a, c, g or t.  
"y" stands for c or t.

<400> 33

gctggatccy tcngngggca tcca

24

<210> 34  
<211> 23  
<212> DNA  
<213> ROS1

<220>  
<223> "n" stands for a, c, g or t.  
"y" stands for c or t.  
"r" stands for a or g.

<400> 34

gcnttyggng argtntayga rgg

23

<210> 35  
<211> 24  
<212> DNA  
<213> CCK4b

<220>  
<223> "n" stands for a, c, g or t.  
"y" stands for c or t.  
"s" stands for c or g.  
"w" stands for a or t.

<400> 35

gctggatccy tcnggnszca tcca

24

<210> 36  
<211> 23  
<212> DNA  
<213> CCK4c

64

&lt;220&gt;

&lt;223&gt; "n" stands for a, c, g or t.

"y" stands for c or t.

"r" stands for a or g.

&lt;400&gt; 36

gagtttyggng argtntttyt ngc

23

&lt;210&gt; 37

&lt;211&gt; 6

&lt;212&gt; PRT

&lt;213&gt; TRK1

&lt;400&gt; 37

Gly Ala Phe Gly Lys Val

1

5

&lt;210&gt; 38

&lt;211&gt; 5

&lt;212&gt; PRT

&lt;213&gt; TRK4

&lt;400&gt; 38

Trp Met Pro Pro Glu

1

5

&lt;210&gt; 39

&lt;211&gt; 8

&lt;212&gt; PRT

&lt;213&gt; ROS1

&lt;400&gt; 39

Ala Phe Gly Glu Val Tyr Glu Gly

1

5

&lt;210&gt; 40

&lt;211&gt; 5

&lt;212&gt; PRT

&lt;213&gt; CCK4b

&lt;400&gt; 40

Trp Met Ser Pro Glu

1

5

65

<210> 41  
<211> 8  
<212> PRT  
<213> CCK4c

<400> 41

Glu Phe Gly Glu Val Tyr Glu Gly  
1 5

<210> 42  
<211> 21  
<212> DNA  
<213> Artificial Sequence

<220>  
<223> Synthesized nucleic acid molecule

<400> 42

cacagaaacg gtcagattca c

21

<210> 43  
<211> 22  
<212> DNA  
<213> Artificial Sequence

<220>  
<223> Synthesized nucleic acid molecule

<400> 43

gatcaggggtg acatcaaggg ac

22

<210> 44  
<211> 22  
<212> DNA  
<213> Artificial Sequence

<220>  
<223> Synthesized nucleic acid molecule

&lt;400&gt; 44

ctcatctgta cacacttcat gg

22

&lt;210&gt; 45

&lt;211&gt; 21

&lt;212&gt; DNA

&lt;213&gt; Artificial Sequence

&lt;220&gt;

&lt;223&gt; Synthesized nucleic acid molecule

&lt;400&gt; 45

gattcccaca ctgtagatgt c

21

&lt;210&gt; 46

&lt;211&gt; 24

&lt;212&gt; DNA

&lt;213&gt; Artificial Sequence

&lt;220&gt;

&lt;223&gt; Synthesized nucleic acid molecule

&lt;400&gt; 46

ggccctcgac tacatccacc acat

24

&lt;210&gt; 47

&lt;211&gt; 24

&lt;212&gt; DNA

&lt;213&gt; Artificial Sequence

&lt;220&gt;

&lt;223&gt; Synthesized nucleic acid molecule

&lt;400&gt; 47

caacgaaact aacacagcat aagg

24

&lt;210&gt; 48

&lt;211&gt; 23

&lt;212&gt; DNA

&lt;213&gt; Artificial Sequence

&lt;220&gt;

67

&lt;223&gt; Synthesized nucleic acid molecule

&lt;400&gt; 48

atggcgaaacg actctcccgc gaa

23

&lt;210&gt; 49

&lt;211&gt; 26

&lt;212&gt; DNA

&lt;213&gt; Artificial Sequence

&lt;220&gt;

&lt;223&gt; Synthesized nucleic acid molecule

&lt;400&gt; 49

acaccaaaat caacaagttt cacctc

26

&lt;210&gt; 50

&lt;211&gt; 23

&lt;212&gt; DNA

&lt;213&gt; Artificial Sequence

&lt;220&gt;

&lt;223&gt; Synthesized nucleic acid molecule

&lt;400&gt; 50

agttacaagc aattccaagt tct

23

&lt;210&gt; 51

&lt;211&gt; 23

&lt;212&gt; DNA

&lt;213&gt; Artificial Sequence

&lt;220&gt;

&lt;223&gt; Synthesized nucleic acid molecule

&lt;400&gt; 51

atgaagagga agaaatcaaa ctg

23

&lt;210&gt; 52

&lt;211&gt; 20

68

&lt;212&gt; DNA

&lt;213&gt; Artificial Sequence

&lt;220&gt;

&lt;223&gt; Synthesized nucleic acid molecule

&lt;400&gt; 52

agatggactg tactgggagg

20

&lt;210&gt; 53

&lt;211&gt; 20

&lt;212&gt; DNA

&lt;213&gt; Artificial Sequence

&lt;220&gt;

&lt;223&gt; Synthesized nucleic acid molecule

&lt;400&gt; 53

actttgtgca gctctgtggg

20

&lt;210&gt; 54

&lt;211&gt; 21

&lt;212&gt; DNA

&lt;213&gt; Artificial Sequence

&lt;220&gt;

&lt;223&gt; Synthesized nucleic acid molecule

&lt;400&gt; 54

aaggttatgg atgtcacagg g

21

&lt;210&gt; 55

&lt;211&gt; 20

&lt;212&gt; DNA

&lt;213&gt; Artificial Sequence

&lt;220&gt;

&lt;223&gt; Synthesized nucleic acid molecule

&lt;400&gt; 55

ctcacaaggt tgccaacagg

20



69

<210> 56  
<211> 21  
<212> DNA  
<213> Artificial Sequence

<220>  
<223> Synthesized nucleic acid molecule

<400> 56

agtccccacc agaaggttta c

21

<210> 57  
<211> 19  
<212> DNA  
<213> Artificial Sequence

<220>  
<223> Synthesized nucleic acid molecule

<400> 57

tcaggggtca gaggtcacg

19

<210> 58  
<211> 21  
<212> DNA  
<213> Artificial Sequence

<220>  
<223> Synthesized nucleic acid molecule

<400> 58

cccaaaccct accacaaatt c

21

<210> 59  
<211> 20  
<212> DNA  
<213> Artificial Sequence

<220>  
<223> Synthesized nucleic acid molecule

<400> 59

cccccggaac acgatgacca

20

<210> 60  
<211> 23  
<212> DNA  
<213> Artificial Sequence

<220>  
<223> Synthesized nucleic acid molecule

<400> 60

agccgctgcc cctcctctac tgt 23

<210> 61  
<211> 23  
<212> DNA  
<213> Artificial Sequence

<220>  
<223> Synthesized nucleic acid molecule

<400> 61

accgcaacat cgccacctac tac 23

<210> 62  
<211> 19  
<212> DNA  
<213> Artificial Sequence

<220>  
<223> Synthesized nucleic acid molecule

<400> 62

ctcgacgtcg tggaccacc 19

<210> 63  
<211> 24  
<212> DNA  
<213> Artificial Sequence

<220>  
<223> Synthesized nucleic acid molecule

<400> 63

caatgttaac ccactctatg tctc 24

<210> 64  
<211> 23  
<212> DNA  
<213> Artificial Sequence

<220>  
<223> Synthesized nucleic acid molecule

<400> 64

agtttgccga tgtttttctt ttc

23

<210> 65  
<211> 19  
<212> DNA  
<213> Artificial Sequence

<220>  
<223> Synthesized nucleic acid molecule

<400> 65

ccgccatgaa ccccggtt

19

<210> 66  
<211> 21  
<212> DNA  
<213> Artificial Sequence

<220>  
<223> Synthesized nucleic acid molecule

<400> 66

cgattgccaa agaccgtgtc a

21

<210> 67  
<211> 23  
<212> DNA  
<213> Artificial Sequence

<220>  
<223> Synthesized nucleic acid molecule

<400> 67

agaagttgca gctgttgaga gga

23

<210> 68  
<211> 21  
<212> DNA  
<213> Artificial Sequence

<220>  
<223> Synthesized nucleic acid molecule

<400> 68

tatggcccggt gtaaggattt c

21

<210> 69  
<211> 23  
<212> DNA  
<213> Artificial Sequence

<220>  
<223> Synthesized nucleic acid molecule

<400> 69

gtgccagaag tggtgtgttg taa

23

<210> 70  
<211> 22  
<212> DNA  
<213> Artificial Sequence

<220>  
<223> Synthesized nucleic acid molecule

<400> 70

tattgaattg gcggaacgga ag

22

<210> 71  
<211> 24  
<212> DNA  
<213> Artificial Sequence

<220>  
<223> Synthesized nucleic acid molecule

<400> 71

ttgttttgtg ctctattcttt ggag

24

73

<210> 72  
<211> 24  
<212> DNA  
<213> Artificial Sequence

<220>  
<223> Synthesized nucleic acid molecule

<400> 72

gattgctttg tgctcattct ttgg

24

<210> 73  
<211> 21  
<212> DNA  
<213> Artificial Sequence

<220>  
<223> Synthesized nucleic acid molecule

<400> 73

ttgttctaag agtgcctcc g

21

<210> 74  
<211> 19  
<212> DNA  
<213> Artificial Sequence

<220>  
<223> Synthesized nucleic acid molecule

<400> 74

aagaccatgc cgtgcgccg

19

<210> 75  
<211> 23  
<212> DNA  
<213> Artificial Sequence

<220>  
<223> Synthesized nucleic acid molecule

<400> 75

74

attccttcag gttctgggta tgg

23

<210> 76  
<211> 19  
<212> DNA  
<213> Artificial Sequence

<220>  
<223> Synthesized nucleic acid molecule

&lt;400&gt; 76

agtcgcgcaa gcctcaatg

19

<210> 77  
<211> 21  
<212> DNA  
<213> Artificial Sequence

<220>  
<223> Synthesized nucleic acid molecule

&lt;400&gt; 77

caccttcagc tgctctatca t

21

<210> 78  
<211> 12  
<212> PRT  
<213> Peptide 540A

&lt;400&gt; 78

His Gly Asp Pro Arg Pro Glu Pro Arg Pro Thr Gln  
1 5 10

<210> 79  
<211> 10  
<212> PRT  
<213> Peptide 539A

&lt;400&gt; 79

Cys Leu Asp Phe Pro Lys Glu Asp Tyr Arg  
1 5 10

75

<210> 80  
<211> 19  
<212> PRT  
<213> Peptide 541A

&lt;400&gt; 80

Asp	Pro	Arg	Thr	Arg	Ala	Ser	Asp	Pro	Gln	Ser	Pro	Pro	Gln	Val	Ser
1				5					10					15	

Arg His Lys

<210> 81  
<211> 14  
<212> PRT  
<213> Peptide 542A

&lt;400&gt; 81

Pro	Ser	Thr	Asn	Arg	Ala	Gly	Ser	Leu	Lys	Asp	Pro	Glu	Cys
1				5					10				

<210> 82  
<211> 15  
<212> PRT  
<213> Peptide 554A

&lt;400&gt; 82

Cys	Leu	Val	Pro	Leu	Ile	Gln	Leu	Tyr	Arg	Lys	Gln	Thr	Ser	Thr
1				5					10					15

<210> 83  
<211> 10  
<212> PRT  
<213> Peptide 579A

&lt;400&gt; 83

Cys	Pro	Leu	Met	Arg	Gln	Asn	Arg	Thr	Arg
1				5					10

<210> 84  
<211> 426

76

&lt;212&gt; PRT

&lt;213&gt; STE20h

&lt;400&gt; 84

Met Ala His Leu Arg Gly Phe Ala Asn Gln His Ser Arg Val Asp Pro  
 1 5 10 15

Glu Glu Leu Phe Thr Lys Leu Asp Arg Ile Gly Lys Gly Ser Phe Gly  
 20 25 30

Glu Val Tyr Lys Gly Ile Asp Asn His Thr Lys Glu Val Val Ala Ile  
 35 40 45

Lys Ile Ile Asp Leu Glu Glu Ala Glu Asp Glu Ile Glu Asp Ile Gln  
 50 55 60

Gln Glu Ile Thr Val Leu Ser Gln Cys Asp Ser Pro Tyr Ile Thr Arg  
 65 70 75 80

Tyr Phe Gly Ser Tyr Leu Lys Ser Thr Lys Leu Trp Ile Ile Met Glu  
 85 90 95

Tyr Leu Gly Gly Gly Ser Ala Leu Asp Leu Leu Lys Pro Gly Pro Leu  
 100 105 110

Glu Glu Thr Tyr Ile Ala Thr Ile Leu Arg Glu Ile Leu Lys Gly Leu  
 115 120 125

Asp Tyr Leu His Ser Glu Arg Lys Ile His Arg Asp Ile Lys Ala Ala  
 130 135 140

Asn Val Leu Leu Ser Glu Gln Gly Asp Val Lys Leu Ala Asp Phe Gly  
 145 150 155 160

Val Ala Gly Gln Leu Thr Asp Thr Gln Ile Lys Arg Asn Thr Phe Val  
 165 170 175

Gly Thr Pro Phe Trp Met Ala Pro Glu Val Ile Lys Gln Ser Ala Tyr  
 180 185 190

Asp Phe Lys Ala Asp Ile Trp Ser Leu Gly Ile Thr Ala Ile Glu Leu  
 195 200 205

Ala Lys Gly Glu Pro Pro Asn Ser Asp Leu His Pro Met Arg Val Leu  
 210 215 220

Phe Leu Ile Pro Lys Asn Ser Pro Pro Thr Leu Glu Gly Gln His Ser  
 225 230 235 240

Lys Pro Phe Lys Glu Phe Val Glu Ala Cys Leu Asn Lys Asp Pro Arg  
 245 250 255

Phe Arg Pro Thr Ala Lys Glu Leu Leu Lys His Lys Phe Ile Thr Arg  
 260 265 270



Tyr Thr Lys Lys Thr Ser Phe Leu Thr Glu Leu Ile Asp Arg Tyr Lys  
           275                                  280                                  285  
 Arg Trp Lys Ser Glu Gly His Gly Glu Glu Ser Ser Ser Glu Asp Ser  
           290                                  295                                  300  
 Asp Ile Asp Gly Glu Ala Glu Asp Gly Glu Gln Gly Pro Ile Trp Thr  
   305                                  310                                  315                                  320  
 Phe Pro Pro Thr Ile Arg Pro Ser Pro His Ser Lys Leu His Lys Gly  
                                   325                                  330                                  335  
 Thr Ala Leu His Ser Ser Gln Lys Pro Ala Glu Pro Val Lys Arg Gln  
                                   340                                  345                                  350  
 Pro Arg Ser Gln Cys Leu Ser Thr Leu Val Arg Pro Val Phe Gly Glu  
                                   355                                  360                                  365  
 Leu Lys Glu Lys His Lys Gln Ser Gly Gly Ser Val Gly Ala Leu Glu  
           370                                  375                                  380  
 Glu Leu Glu Asn Ala Phe Ser Leu Ala Glu Glu Ser Cys Pro Gly Ile  
   385                                  390                                  395                                  400  
 Ser Asp Lys Leu Met Val His Leu Val Glu Arg Val Gln Arg Phe Ser  
                                   405                                  410                                  415  
 His Asn Arg Asn His Leu Thr Ser Thr Arg  
                                   420                                  425

<210> 85  
 <211> 431  
 <212> PRT  
 <213> MST3

<400> 85

Met Ala His Ser Pro Val Gln Ser Gly Leu Pro Gly Met Gln Asn Leu  
   1                                  5                                  10                                  15  
 Lys Ala Asp Pro Glu Glu Leu Phe Thr Lys Leu Glu Lys Ile Gly Lys  
           20                                  25                                  30  
 Gly Ser Phe Gly Glu Val Phe Lys Gly Ile Asp Asn Arg Thr Gln Lys  
           35                                  40                                  45  
 Val Val Ala Ile Lys Ile Ile Asp Leu Glu Glu Ala Glu Asp Glu Ile  
   50                                  55                                  60  
 Glu Asp Ile Gln Gln Glu Ile Thr Val Leu Ser Gln Cys Asp Ser Pro  
   65                                  70                                  75                                  80  
 Tyr Val Thr Lys Tyr Tyr Gly Ser Tyr Leu Lys Asp Thr Lys Leu Trp

78

85 90 95

Ile Ile Met Glu Tyr Leu Gly Gly Gly Ser Ala Leu Asp Leu Leu Glu  
100 105 110

Pro Gly Pro Leu Asp Glu Thr Gln Ile Ala Thr Ile Leu Arg Glu Ile  
115 120 125

Leu Lys Gly Leu Asp Tyr Leu His Ser Glu Lys Lys Ile His Arg Asp  
130 135 140

Ile Lys Ala Ala Asn Val Leu Leu Ser Glu His Gly Glu Val Lys Leu  
145 150 155 160

Ala Asp Phe Gly Val Ala Gly Gln Leu Thr Asp Thr Gln Ile Lys Arg  
165 170 175

Asn Thr Phe Val Gly Thr Pro Phe Trp Met Ala Pro Glu Val Ile Lys  
180 185 190

Gln Ser Ala Tyr Asp Ser Lys Ala Asp Ile Trp Ser Leu Gly Ile Thr  
195 200 205

Ala Ile Glu Leu Ala Arg Gly Glu Pro Pro His Ser Glu Leu His Pro  
210 215 220

Met Lys Val Leu Phe Leu Ile Pro Lys Asn Asn Pro Pro Thr Leu Glu  
225 230 235 240

Gly Asn Tyr Ser Lys Pro Leu Lys Glu Phe Val Glu Ala Cys Leu Asn  
245 250 255

Lys Glu Pro Ser Phe Arg Pro Thr Ala Lys Glu Leu Leu Lys His Lys  
260 265 270

Phe Ile Leu Arg Asn Ala Lys Lys Thr Ser Tyr Leu Thr Glu Leu Ile  
275 280 285

Asp Arg Tyr Lys Arg Trp Lys Ala Glu Gln Ser His Asp Asp Ser Ser  
290 295 300

Ser Glu Asp Ser Asp Ala Glu Thr Asp Gly Gln Ala Ser Gly Gly Ser  
305 310 315 320

Asp Ser Gly Asp Trp Ile Phe Thr Ile Arg Glu Lys Asp Pro Lys Asn  
325 330 335

Leu Glu Asn Gly Ala Leu Gln Pro Ser Asp Leu Asp Arg Asn Lys Met  
340 345 350

Lys Asp Ile Pro Lys Arg Pro Phe Ser Gln Cys Leu Ser Thr Ile Ile  
355 360 365

Ser Pro Leu Phe Ala Glu Leu Lys Glu Lys Ser Gln Ala Cys Gly Gly  
370 375 380

Asn Leu Gly Ser Ile Glu Glu Leu Arg Gly Ala Ile Tyr Leu Ala Glu  
385 390 395 400

Glu Ala Cys Pro Gly Ile Ser Asp Thr Met Val Ala Gln Leu Val Gln  
405 410 415

Arg Leu Gln Arg Tyr Ser Leu Ser Gly Gly Gly Thr Ser Ser His  
420 425 430

<210> 86

<211> 443

<212> PRT

<213> T19A5.2\_ce

<220>

<223> "Xaa" stands for any amino acid.

<400> 86

Met Thr Thr Thr Ser Ser Asp Glu Leu Pro Arg Gln Ala Asp Asp Asp  
1 5 10 15

Ser Met Lys Trp Asp Arg Ile Tyr Ile Gln Lys Leu Asp Pro Glu Val  
20 25 30

Ile Phe Thr Lys Gln Glu Arg Ile Gly Arg Gly Ser Phe Gly Glu Val  
35 40 45

Tyr Lys Gly Ile Asp Asn Arg Thr Gly Arg Val Val Ala Ile Lys Ile  
50 55 60

Ile Asp Leu Glu Gln Ala Glu Asp Glu Ile Glu Asp Ile Gln Gln Glu  
65 70 75 80

Ile Gln Val Leu Ser Gln Cys Asp Ser Gln Tyr Val Thr Lys Tyr Phe  
85 90 95

Gly Ser Phe Leu Lys Gly Ser Lys Leu Trp Ile Ile Met Glu Tyr Leu  
100 105 110

Gly Gly Gly Ser Ala Leu Asp Leu Thr Lys Ser Gly Lys Leu Asp Glu  
115 120 125

Ser His Ile Ala Val Ile Leu Arg Glu Ile Leu Lys Gly Leu Glu Tyr  
130 135 140

Leu His Ser Glu Arg Lys Ile His Arg Asp Ile Lys Ala Ala Asn Val  
145 150 155 160

Leu Val Ser Glu His Gly Asp Val Lys Val Ala Asp Phe Gly Val Ala  
165 170 175

80

Gly Gln Leu Thr Glu Thr Val Lys Lys Arg Ile Thr Phe Val Gly Ser  
 180 185 190

Pro Phe Trp Met Ala Pro Glu Leu Ile Lys Gln Ser Ser Tyr Asp Tyr  
 195 200 205

Lys Ala Asp Ile Trp Ser Leu Gly Ile Thr Ala Ile Glu Leu Ala Asn  
 210 215 220

Gly Glu Pro Pro His Ser Asp Leu His Pro Met Arg Val Leu Phe Leu  
 225 230 235 240

Ile Pro Lys Asn Pro Pro Pro Val Leu Gln Gly Ser Gln Trp Ser Lys  
 245 250 255

Pro Phe Lys Glu Phe Val Glu Met Cys Leu Asn Lys Asp Pro Glu Asn  
 260 265 270

Arg Pro Ser Ala Ser Thr Leu Leu Lys His Gln Phe Ile Lys Arg Ala  
 275 280 285

Lys Lys Asn Ser Ile Leu Val Asp Leu Ile Glu Arg Ala Ala Glu Tyr  
 290 295 300

Arg Leu Arg Thr Gly Val Ser Ser Asp Ser Asp Leu Asp Glu Asp Ser  
 305 310 315 320

Asp Gly Gly Gly Gly Thr Ser Lys Trp Asp Tyr Pro Thr Val Arg Gly  
 325 330 335

Pro Arg Val Ser Ala Asp Asp Asp Gly Thr Val Arg Gln Arg Thr Asp  
 340 345 350

Arg Pro Arg Ala Gln Val Asp Arg Arg Ser Pro Ser Gly Ser Pro Gly  
 355 360 365

Gly Thr Ile Val Arg Gly Ser Pro Gln Val Ala Ala Val Ala Glu Gln  
 370 375 380

Leu Arg Asn Ser Xaa Xaa Ala Leu Asp Gln Leu Arg His Val Phe Arg  
 385 390 395 400

Asp Val Glu Asp Ser Cys Pro Gly Ile Cys Asn Glu Leu Ile Glu Glu  
 405 410 415

Leu Met Gln Arg Ile Ala Val Pro Gln Val Ser Gln Ser Asp Leu Asp  
 420 425 430

Ala Ala Ile Arg Arg Leu Thr Thr Pro Pro Ser  
 435 440

&lt;210&gt; 87

<211> 275  
 <212> PRT  
 <213> Pak\_sp

<400> 87

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Leu Leu Tyr Arg Asn Phe Val Lys Ile Gly Gln Gly Ala Ser Gly Asp
 1              5              10              15

Val Tyr Ser Ala Arg Gln Val Gly Thr Asn Leu Ser Val Ala Ile Lys
      20              25              30

Lys Met Asn Ile Asn Gln Gln Pro Lys Lys Glu Phe Ile Val Asn Glu
      35              40              45

Ile Leu Val Met Lys Ser His His His Lys Asn Ile Val Asn Phe Ile
 50              55              60

Asp Thr Phe Phe Tyr Lys Ser Glu Leu Trp Met Val Met Glu Tyr Met
65              70              75              80

Arg Gly Gly Ser Leu Thr Glu Val Val Thr Asn Asn Thr Leu Ser Glu
      85              90              95

Gly Gln Ile Ala Ala Ile Cys Lys Glu Thr Leu Glu Gly Leu Gln His
      100              105              110

Leu His Glu Asn Gly Ile Val His Arg Asp Ile Lys Ser Asp Asn Ile
 115              120              125

Leu Leu Ser Leu Gln Gly Asp Ile Lys Leu Thr Asp Phe Gly Phe Cys
 130              135              140

Ala Gln Ile Asp Ser Asn Met Thr Lys Arg Thr Thr Met Val Gly Thr
145              150              155              160

Pro Tyr Trp Met Ala Pro Glu Val Val Thr Arg Lys Glu Tyr Gly Phe
      165              170              175

Lys Val Asp Val Trp Ser Leu Gly Ile Met Ala Ile Glu Met Val Glu
 180              185              190

Gly Glu Pro Pro Tyr Leu Asn Glu Asn Pro Leu Arg Ala Leu Tyr Leu
 195              200              205

Ile Ala Thr Ile Gly Thr Pro Lys Ile Ser Arg Pro Glu Leu Leu Ser
 210              215              220

Ser Val Phe His Asp Phe Leu Ser Lys Ser Leu Thr Val Asn Pro Lys
225              230              235              240

Gln Arg Pro Ser Ser Gly Glu Leu Leu Arg His Pro Phe Leu Lys Gln
      245              250              255

Ala Val Pro Val Ser Ser Leu Ile Pro Leu Ile Lys Ser Ile His His
 260              265              270

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Ser Gly Lys  
275

<210> 88  
<211> 1109  
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<213> ZC504.4\_ce

<400> 88

Met	Ser	Ser	Ser	Gly	Leu	Asp	Glu	Ile	Asp	Leu	Asn	Ser	Leu	Arg	Asp	1	5	10	15
Pro	Ala	Gly	Ile	Phe	Glu	Leu	Ile	Glu	Val	Val	Gly	Asn	Gly	Thr	Tyr	20	25	30	
Gly	Gln	Val	Tyr	Lys	Gly	Arg	His	Val	Lys	Thr	Ala	Gln	Leu	Ala	Ala	35	40	45	
Ile	Lys	Ile	Met	Asn	Ile	Asn	Glu	Asp	Glu	Glu	Asp	Glu	Ile	Lys	Leu	50	55	60	
Glu	Ile	Asn	Met	Leu	Lys	Lys	His	Ser	His	His	Arg	Asn	Val	Ala	Thr	65	70	75	80
Tyr	Tyr	Gly	Ala	Phe	Ile	Lys	Lys	Leu	Pro	Ser	Ser	Thr	Gly	Lys	His	85	90	95	
Asp	Gln	Leu	Trp	Leu	Val	Met	Glu	Phe	Cys	Gly	Ser	Gly	Ser	Ile	Thr	100	105	110	
Asp	Leu	Val	Lys	Asn	Thr	Lys	Gly	Gly	Ser	Leu	Lys	Glu	Glu	Trp	Ile	115	120	125	
Ala	Tyr	Ile	Cys	Arg	Glu	Ile	Leu	Arg	Gly	Leu	Tyr	His	Leu	His	Gln	130	135	140	
Ser	Lys	Val	Ile	His	Arg	Asp	Ile	Lys	Gly	Gln	Asn	Val	Leu	Leu	Thr	145	150	155	160
Asp	Ser	Ala	Glu	Val	Lys	Leu	Val	Asp	Phe	Gly	Val	Ser	Ala	Gln	Leu	165	170	175	
Asp	Lys	Thr	Val	Gly	Arg	Arg	Asn	Thr	Phe	Ile	Gly	Thr	Pro	Tyr	Trp	180	185	190	
Met	Ala	Pro	Glu	Val	Ile	Ala	Cys	Asp	Glu	Ser	Pro	Glu	Ala	Thr	Tyr	195	200	205	
Asp	Ser	Arg	Ser	Asp	Leu	Trp	Ser	Leu	Gly	Ile	Thr	Ala	Leu	Glu	Met	210	215	220	

Ala Glu Gly His Pro Pro Leu Cys Asp Met His Pro Met Arg Ala Leu  
 225 230 235 240  
 Phe Leu Ile Pro Arg Asn Pro Pro Pro Lys Leu Lys Arg Asn Lys Lys  
 245 250 255  
 Trp Thr Lys Lys Phe Glu Thr Phe Ile Glu Thr Val Leu Val Lys Asp  
 260 265 270  
 Tyr His Gln Arg Pro Tyr Thr Gly Ala Leu Leu Arg His Pro Phe Ile  
 275 280 285  
 Lys Glu Gln Pro His Glu Gln Thr Ile Arg His Ser Ile Lys Glu His  
 290 295 300  
 Ile Asp Arg Asn Arg Arg Val Lys Lys Asp Asp Ala Asp Tyr Glu Tyr  
 305 310 315 320  
 Ser Gly Ser Glu Asp Asp Glu Pro Ser Pro Asn Asn Arg Asp Asp Ser  
 325 330 335  
 Glu Ser Ser Ser Met Ile Pro Met Asp Asn Thr Leu Arg Lys Gly Phe  
 340 345 350  
 Gln Lys Leu Gln Glu Ser Ser Arg Gly Phe Ala Glu Pro Gly Ala Gln  
 355 360 365  
 Gln Leu Arg Arg Leu Pro Gln Gln Pro Ala Pro Ala Pro Phe Gln Tyr  
 370 375 380  
 Gln Gln Ser Arg Tyr Val Glu Pro Arg Arg Glu Ser Ser Glu Val Lys  
 385 390 395 400  
 Leu Arg Ala Val Ser Ser Arg Gly Ala Ala Asp Gly Pro Arg His Ser  
 405 410 415  
 Pro Ala Ser Arg Pro Arg Pro Arg Ser Pro Gln Gln Ser His Pro Ala  
 420 425 430  
 Ala Pro His Leu Ala Asp Leu Ala Asn Tyr Glu Lys Arg Arg Arg Ser  
 435 440 445  
 Glu Arg Glu Glu Arg Arg Glu Arg Glu Arg Gln Ala His His Ala Met  
 450 455 460  
 Pro Ile Ala Arg Val Ser Ala Ser Val Pro Ala Pro Gln Gln Ser Arg  
 465 470 475 480  
 Lys Met Ser Glu Pro Leu Leu Ile Thr His Val Lys Pro Glu Asp Leu  
 485 490 495  
 Asp Val Leu Ala Ser Glu Leu Ser Lys Met Gly Gly His His Asn Gly  
 500 505 510  
 Arg Ser Arg Glu Glu Ser Met Ser Pro Pro Pro Pro Ala Pro Pro Pro

515	520	525
Arg Glu Ala Ser Ile Ser Ser Ile Thr Asp Thr Ile Asp Val Gly Glu		
530	535	540
Leu Asp Asn Gly Ala Asp Ala Glu Trp Asp Asp Leu Lys Asp Ile Met		
545	550	555
Met Asn Gly Glu Gly Thr Leu Arg Gly Pro Asn Lys Pro Leu Pro Pro		
	565	570
Thr Pro Thr Asp Gly Glu Asn Thr Leu Val Ser Asp Val Arg Arg Asn		
	580	585
Gly Asn Gly Asn Ser Gly His Gly Ala Tyr Lys Gly Lys Lys Ile Pro		
	595	600
Glu Ile Arg Pro Gly Ile Ile Ser Leu Asp Asp Asp Asp Ser Asp Ser		
610	615	620
Asp Asn Glu Glu Gly Asn Glu Pro Leu Met Phe Lys Pro Ile Val Arg		
625	630	635
Cys Pro Phe Ser Ile Phe Phe Trp Phe Leu Ser Ala Asn Val Ile His		
	645	650
Ser Val Asp Gly Ser Ile Pro Leu Val Lys His Leu Ile Trp Phe Gln		
	660	665
Asn Ala Ser Ser Ser Arg Gly Ala Leu Pro Asp Leu Leu Pro Lys Ser		
	675	680
Pro Asp Leu Arg Arg Gln Ile Asn Asp Gln Thr Arg Gln Met Ser Asp		
690	695	700
Asp Arg Ala Asp Glu Gln Pro Asn Gly Phe Gln Asn Ser Asp Ser Arg		
705	710	715
Ser Ser Ile Gln His Ser Phe Ser Asn Arg Asp Arg Glu Lys Ser Phe		
	725	730
Val Gly Tyr Phe Gly Gly Gly Ala Gly Ala Gly Gly Gly Thr Val Asn		
	740	745
Arg Pro Gly Arg Pro Gln Asp Ile Asn Gln Val Gln Val Asn Val Thr		
	755	760
Pro Asn Ser Asn Gly Thr Pro Ala Glu Asn Asp Ala Pro Glu Ile Arg		
	770	775
Lys Tyr Lys Lys Lys Phe Ser Gly Glu Ile Leu Cys Ala Ala Leu Trp		
785	790	795
Gly Val Asn Leu Leu Ile Gly Thr Asp Ser Gly Leu Met Leu Leu Asp		
	805	810
		815



Arg Ser Gly Gln Gly Lys Val Tyr Pro Leu Ile Ser Arg Arg Arg Phe  
 820 825 830  
 Asp Gln Met Thr Val Leu Glu Gly Gln Asn Ile Leu Ala Thr Ile Ser  
 835 840 845  
 Gly Arg Lys Arg Arg Ile Arg Val Tyr Tyr Leu Ser Trp Leu Arg Gln  
 850 855 860  
 Lys Ile Leu Arg Thr Glu Gly Ala Gly Ser Ala Asn Thr Thr Glu Lys  
 865 870 875 880  
 Arg Asn Gly Trp Val Asn Val Gly Asp Leu Gln Gly Ala Ile His Phe  
 885 890 895  
 Lys Ile Val Arg Tyr Glu Arg Ile Lys Phe Leu Val Val Gly Leu Glu  
 900 905 910  
 Ser Ser Ile Glu Ile Tyr Ala Trp Ala Pro Lys Pro Tyr His Lys Phe  
 915 920 925  
 Met Ser Phe Lys Ser Phe Gly Ser Leu Ser His Val Pro Leu Ile Val  
 930 935 940  
 Asp Leu Thr Val Glu Asp Asn Ala Arg Leu Lys Val Leu Tyr Gly Ser  
 945 950 955 960  
 Thr Gly Gly Phe His Ala Ile Asp Leu Asp Ser Ala Ala Val Tyr Asp  
 965 970 975  
 Ile Tyr Thr Pro Ala Gln Ser Gly Gln Thr Thr Thr Pro His Cys Ile  
 980 985 990  
 Val Val Leu Pro Asn Ser Asn Gly Met Gln Leu Leu Leu Cys Tyr Asp  
 995 1000 1005  
 Asn Glu Gly Val Tyr Val Asn Thr Tyr Gly Arg Met Thr Lys Asn Val  
 1010 1015 1020  
 Val Leu Gln Trp Gly Glu Met Pro Ser Ser Val Ala Tyr Ile Ser Thr  
 1025 1030 1035 1040  
 Gly Gln Ile Met Gly Trp Gly Asn Lys Ala Ile Glu Ile Arg Ser Val  
 1045 1050 1055  
 Asp Thr Gly His Leu Asp Gly Val Phe Met His Lys Lys Ala Gln Lys  
 1060 1065 1070  
 Leu Lys Phe Leu Cys Glu Arg Asn Asp Lys Val Phe Phe Ser Ser Ala  
 1075 1080 1085  
 Lys Gly Gly Gly Ser Cys Gln Ile Tyr Phe Met Thr Leu Asn Lys Pro  
 1090 1095 1100

Gly Leu Thr Asn Trp  
1105

<210> 89  
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<213> NIK\_m

<400> 89

Met	Ala	Asn	Asp	Ser	Pro	Ala	Lys	Ser	Leu	Val	Asp	Ile	Asp	Leu	Ser	1	5	10	15
Ser	Leu	Arg	Asp	Pro	Ala	Gly	Ile	Phe	Glu	Leu	Val	Glu	Val	Val	Gly	20	25	30	
Asn	Gly	Thr	Tyr	Gly	Gln	Val	Tyr	Lys	Gly	Arg	His	Val	Lys	Thr	Val	35	40	45	
Thr	Ala	Ala	Ile	Lys	Val	Met	Asp	Val	Thr	Glu	Asp	Glu	Glu	Glu	Glu	50	55	60	
Ile	Thr	Leu	Glu	Ile	Asn	Met	Leu	Lys	Lys	Tyr	Ser	His	His	Arg	Asn	65	70	75	80
Ile	Ala	Thr	Tyr	Tyr	Gly	Ala	Phe	Ile	Lys	Lys	Ser	Pro	Pro	Gly	His	85	90	95	
Asp	Asp	Gln	Leu	Trp	Leu	Val	Met	Glu	Phe	Cys	Gly	Ala	Gly	Ser	Ile	100	105	110	
Thr	Asp	Leu	Val	Lys	Asn	Thr	Lys	Gly	Asn	Thr	Leu	Lys	Glu	Asp	Trp	115	120	125	
Ile	Ala	Tyr	Ile	Ser	Arg	Glu	Ile	Leu	Arg	Gly	Leu	Ala	His	Leu	His	130	135	140	
Ile	His	His	Val	Ile	His	Arg	Asp	Ile	Lys	Gly	Gln	Asn	Val	Leu	Leu	145	150	155	160
Thr	Glu	Asn	Ala	Glu	Val	Lys	Leu	Val	Asp	Phe	Gly	Val	Ser	Ala	Gln	165	170	175	
Leu	Asp	Arg	Thr	Val	Gly	Arg	Arg	Asn	Thr	Phe	Ile	Gly	Thr	Pro	Tyr	180	185	190	
Trp	Met	Ala	Pro	Glu	Val	Ile	Ala	Cys	Asp	Glu	Asn	Pro	Asp	Ala	Thr	195	200	205	
Tyr	Asp	Tyr	Arg	Ser	Asp	Leu	Trp	Ser	Cys	Gly	Ile	Thr	Ala	Ile	Glu	210	215	220	
Met	Ala	Glu	Gly	Gly	Pro	Pro	Leu	Cys	Asp	Met	His	Pro	Met	Arg	Ala				

225		230		235		240
Leu Phe Leu Ile Pro Arg Asn Pro Pro Pro Arg Leu Lys Ser Lys Lys						
		245		250		255
Trp Ser Lys Lys Phe Phe Ser Phe Ile Glu Gly Cys Leu Val Lys Asn						
		260		265		270
Tyr Met Gln Arg Pro Ser Thr Glu Gln Leu Leu Lys His Pro Phe Ile						
		275		280		285
Arg Asp Gln Pro Asn Glu Arg Gln Val Arg Ile Gln Leu Lys Asp His						
		290		295		300
Ile Asp Arg Thr Arg Lys Lys Arg Gly Glu Lys Asp Glu Thr Glu Tyr						
305		310		315		320
Glu Tyr Ser Gly Ser Glu Glu Glu Glu Glu Val Pro Glu Gln Glu						
		325		330		335
Gly Glu Pro Ser Ser Ile Val Asn Val Pro Gly Glu Ser Thr Leu Arg						
		340		345		350
Arg Asp Phe Leu Arg Leu Gln Gln Glu Asn Lys Glu Arg Ser Glu Ala						
		355		360		365
Leu Arg Arg Gln Gln Leu Leu Gln Glu Gln Gln Leu Arg Glu Gln Glu						
		370		375		380
Glu Tyr Lys Arg Gln Leu Leu Ala Glu Arg Gln Lys Arg Ile Glu Gln						
385		390		395		400
Gln Lys Glu Gln Arg Arg Arg Leu Glu Glu Gln Gln Arg Arg Glu Arg						
		405		410		415
Glu Ala Arg Arg Gln Gln Glu Arg Glu Gln Arg Arg Arg Glu Gln Glu						
		420		425		430
Glu Lys Arg Arg Leu Glu Glu Leu Glu Arg Arg Arg Lys Glu Glu Glu						
		435		440		445
Glu Arg Arg Arg Ala Glu Glu Glu Lys Arg Arg Val Glu Arg Glu Gln						
		450		455		460
Glu Tyr Ile Arg Arg Gln Leu Glu Glu Glu Gln Arg His Leu Glu Ile						
465		470		475		480
Leu Gln Gln Gln Leu Leu Gln Glu Gln Ala Met Leu Leu His Asp His						
		485		490		495
Arg Arg Pro His Ala Gln Gln Gln Pro Pro Pro Pro Gln Gln Gln Asp						
		500		505		510
Arg Ser Lys Pro Ser Phe His Ala Pro Glu Pro Lys Pro His Tyr Asp						
		515		520		525

Pro Ala Asp Arg Ala Arg Glu Val Gln Trp Ser His Leu Ala Ser Leu  
 530 535 540  
 Lys Asn Asn Val Ser Pro Val Ser Arg Ser His Ser Phe Ser Asp Pro  
 545 550 555 560  
 Ser Pro Lys Phe Ala His His His Leu Arg Ser Gln Asp Pro Cys Pro  
 565 570 575  
 Pro Ser Arg Ser Glu Gly Leu Ser Gln Ser Ser Asp Ser Lys Ser Glu  
 580 585 590  
 Val Pro Glu Pro Thr Gln Lys Ala Trp Ser Arg Ser Asp Ser Asp Glu  
 595 600 605  
 Val Pro Pro Arg Val Pro Val Arg Thr Thr Ser Arg Ser Pro Val Leu  
 610 615 620  
 Ser Arg Arg Asp Ser Pro Leu Gln Gly Gly Gly Gln Gln Asn Ser Gln  
 625 630 635 640  
 Ala Gly Gln Arg Asn Ser Thr Ser Ser Ile Glu Pro Arg Leu Leu Trp  
 645 650 655  
 Glu Arg Val Glu Lys Leu Val Pro Arg Pro Gly Ser Gly Ser Ser Ser  
 660 665 670  
 Gly Ser Ser Asn Ser Gly Ser Gln Pro Gly Ser His Pro Gly Ser Gln  
 675 680 685  
 Ser Gly Ser Gly Glu Arg Phe Arg Val Arg Ser Ser Ser Lys Ser Glu  
 690 695 700  
 Gly Ser Pro Ser Pro Arg Gln Glu Ser Ala Ala Lys Lys Pro Asp Asp  
 705 710 715 720  
 Lys Lys Glu Val Phe Arg Ser Leu Lys Pro Ala Gly Glu Val Asp Leu  
 725 730 735  
 Thr Ala Leu Ala Lys Glu Leu Arg Ala Val Glu Asp Val Arg Pro Pro  
 740 745 750  
 His Lys Val Thr Asp Tyr Ser Ser Ser Ser Glu Glu Ser Gly Thr Thr  
 755 760 765  
 Asp Glu Glu Glu Glu Asp Val Glu Gln Glu Gly Ala Asp Asp Ser Thr  
 770 775 780  
 Ser Gly Pro Glu Asp Thr Arg Ala Ala Ser Ser Pro Asn Leu Ser Asn  
 785 790 795 800  
 Gly Glu Thr Glu Ser Val Lys Thr Met Ile Val His Asp Asp Val Glu  
 805 810 815

Ser Glu Pro Ala Met Thr Pro Ser Lys Glu Gly Thr Leu Ile Val Arg  
 820 825 830

Gln Thr Gln Ser Ala Ser Ser Thr Leu Gln Lys His Lys Ser Ser Ser  
 835 840 845

Ser Phe Thr Pro Phe Ile Asp Pro Arg Leu Leu Gln Ile Ser Pro Ser  
 850 855 860

Ser Gly Thr Thr Val Thr Ser Val Val Gly Phe Ser Cys Asp Gly Leu  
 865 870 875 880

Arg Pro Glu Ala Ile Arg Gln Asp Pro Thr Arg Lys Gly Ser Val Val  
 885 890 895

Asn Val Asn Pro Thr Asn Thr Arg Pro Gln Ser Asp Thr Pro Glu Ile  
 900 905 910

Arg Lys Tyr Lys Lys Arg Phe Asn Ser Glu Ile Leu Cys Ala Ala Leu  
 915 920 925

Trp Gly Val Asn Leu Leu Val Gly Thr Glu Ser Gly Leu Met Leu Leu  
 930 935 940

Asp Arg Ser Gly Gln Gly Lys Val Tyr Pro Leu Ile Ser Arg Arg Arg  
 945 950 955 960

Phe Gln Gln Met Asp Val Leu Glu Gly Leu Asn Val Leu Val Thr Ile  
 965 970 975

Ser Gly Lys Lys Asp Lys Leu Arg Val Tyr Tyr Leu Ser Trp Leu Arg  
 980 985 990

Asn Lys Ile Leu His Asn Asp Pro Glu Val Glu Lys Lys Gln Gly Trp  
 995 1000 1005

Thr Thr Val Gly Asp Leu Glu Gly Cys Val His Tyr Lys Val Val Lys  
 1010 1015 1020

Tyr Glu Arg Ile Lys Phe Leu Val Ile Ala Leu Lys Ser Ser Val Glu  
 1025 1030 1035 1040

Val Tyr Ala Trp Ala Pro Lys Pro Tyr His Lys Phe Met Ala Phe Lys  
 1045 1050 1055

Ser Phe Gly Glu Leu Leu His Lys Pro Leu Leu Val Asp Leu Thr Val  
 1060 1065 1070

Glu Glu Gly Gln Arg Leu Lys Val Ile Tyr Gly Ser Cys Ala Gly Phe  
 1075 1080 1085

His Ala Val Asp Val Asp Ser Gly Ser Val Tyr Asp Ile Tyr Leu Pro  
 1090 1095 1100

90

Thr His Ile Gln Cys Ser Ile Lys Pro His Ala Ile Ile Ile Leu Pro  
 1105 1110 1115 1120  
 Asn Thr Asp Gly Met Glu Leu Leu Val Cys Tyr Glu Asp Glu Gly Val  
 1125 1130 1135  
 Tyr Val Asn Thr Tyr Gly Arg Ile Thr Lys Asp Val Val Leu Gln Trp  
 1140 1145 1150  
 Gly Glu Met Pro Thr Ser Val Ala Tyr Ile Arg Ser Asn Gln Thr Met  
 1155 1160 1165  
 Gly Trp Gly Glu Lys Ala Ile Glu Ile Arg Ser Val Glu Thr Gly His  
 1170 1175 1180  
 Leu Asp Gly Val Phe Met His Lys Arg Ala Gln Arg Leu Lys Phe Leu  
 1185 1190 1195 1200  
 Cys Gly Arg Asn Asp Lys Val Phe Phe Ser Ser Val Arg Ser Gly Gly  
 1205 1210 1215  
 Ser Ser Gln Val Tyr Phe Met Thr Leu Gly Arg Thr Ser Leu Leu Ser  
 1220 1225 1230  
 Trp

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 <212> PRT  
 <213> SULLU\_ce

<400> 90

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 1 5 10 15  
 Ile Ala Ala Leu Phe Ser Asn Lys Asp Pro Glu Gln Arg Tyr Gln Asp  
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 Leu Arg Glu Ile Gly His Gly Ser Phe Gly Ala Val Tyr Phe Ala Tyr  
 35 40 45  
 Asp Lys Lys Asn Glu Gln Thr Val Ala Ile Lys Lys Met Asn Phe Ser  
 50 55 60  
 Gly Lys Gln Ala Val Glu Lys Trp Asn Asp Ile Leu Lys Glu Val Ser  
 65 70 75 80  
 Phe Leu Asn Thr Val Val His Pro His Ile Val Asp Tyr Lys Ala Cys  
 85 90 95  
 Phe Leu Lys Asp Thr Thr Cys Trp Leu Val Met Glu Tyr Cys Ile Gly  
 100 105 110

Ser Ala Ala Asp Ile Val Asp Val Leu Arg Lys Gly Met Arg Glu Val  
 115 120 125  
 Glu Ile Ala Ala Ile Cys Ser Gln Thr Leu Asp Ala Leu Arg Tyr Leu  
 130 135 140  
 His Ser Leu Lys Arg Ile His Arg Asp Ile Lys Ala Gly Asn Ile Leu  
 145 150 155 160  
 Leu Ser Asp His Ala Ile Val Lys Leu Ala Asp Phe Gly Ser Ala Ser  
 165 170 175  
 Leu Val Asp Pro Ala Gln Thr Phe Ile Gly Thr Pro Phe Phe Met Ala  
 180 185 190  
 Pro Glu Val Ile Leu Ala Met Asp Glu Gly His Tyr Thr Asp Arg Ala  
 195 200 205  
 Asp Ile Trp Ser Leu Gly Ile Thr Cys Ile Glu Leu Ala Glu Arg Arg  
 210 215 220  
 Pro Pro Leu Phe Ser Met Asn Ala Met Ser Ala Leu Tyr His Ile Ala  
 225 230 235 240  
 Gln Asn Asp Pro Pro Thr Leu Ser Pro Ile Asp Thr Ser Glu Gln Pro  
 245 250 255  
 Glu Trp Ser Leu Glu Phe Val Gln Phe Ile Asp Lys Cys Leu Arg Lys  
 260 265 270  
 Pro Ala Glu Glu Arg Met Ser Ala Glu Glu Cys Phe Arg His Pro Phe  
 275 280 285  
 Ile Gln Arg Ser Arg Pro Ser Asp Thr Ile Gln Glu Leu Ile Gln Arg  
 290 295 300  
 Thr Lys Asn Met Val Leu Glu Leu Asp Asn Phe Gln Tyr Lys Lys Met  
 305 310 315 320  
 Arg Lys Leu Met Tyr Leu Asp Glu Thr Glu Gly Lys Glu Gly Ser Glu  
 325 330 335  
 Gly Asn Gly Ala Ser Asp Asp Leu Asp Phe His Gly Asn Glu Ala Asn  
 340 345 350  
 Ser Ile Gly Arg Ala Gly Asp Ser Ala Ser Ser Arg Ser Ala Ser Leu  
 355 360 365  
 Thr Ser Phe Arg Ser Met Gln Ser Ser Gly Gly Ala Gly Leu Leu Val  
 370 375 380  
 Ser Thr Asn Thr Thr Gly Ala Met Asp Asn Val His Gly Ser Ser Gly  
 385 390 395 400  
 Tyr Gly Asn Gly Ser Ser Ser Thr Thr Ser Ser Ala Arg Arg Arg Pro  
 405 410 415

Pro Ile Pro Ser Gln Met Leu Ser Ser Thr Ser Thr Ser Gly Val Gly  
 420 425 430  
 Thr Met Pro Ser His Gly Ser Val Gly Ala Ser Ile Thr Ala Ile Ala  
 435 440 445  
 Val Asn Pro Thr Pro Ser Pro Ser Glu Pro Ile Pro Thr Ser Gln Pro  
 450 455 460  
 Thr Ser Lys Ser Glu Ser Ser Ser Ile Leu Glu Thr Ala His Asp Asp  
 465 470 475 480  
 Pro Leu Asp Thr Ser Ile Arg Ala Pro Val Lys Asp Leu His Met Pro  
 485 490 495  
 His Arg Ala Val Lys Glu Arg Ile Ala Thr Leu Gln Asn His Lys Phe  
 500 505 510  
 Ala Thr Leu Arg Ser Gln Arg Ile Ile Asn Gln Glu Gln Glu Glu Tyr  
 515 520 525  
 Thr Lys Glu Asn Asn Met Tyr Glu Gln Met Ser Lys Tyr Lys His Leu  
 530 535 540  
 Arg Gln Ala His His Lys Glu Leu Gln Gln Phe Glu Glu Arg Cys Ala  
 545 550 555 560  
 Leu Asp Arg Glu Gln Leu Arg Val Lys Met Asp Arg Glu Leu Glu Gln  
 565 570 575  
 Leu Thr Thr Thr Tyr Ser Lys Glu Lys Met Arg Val Arg Cys Ser Gln  
 580 585 590  
 Asn Asn Glu Leu Asp Lys Arg Lys Lys Asp Ile Glu Asp Gly Glu Lys  
 595 600 605  
 Lys Met Lys Lys Thr Lys Asn Ser Gln Asn Gln Gln Gln Met Lys Leu  
 610 615 620  
 Tyr Ser Ala Gln Gln Leu Lys Glu Tyr Lys Tyr Asn Lys Glu Ala Gln  
 625 630 635 640  
 Lys Thr Arg Leu Arg Ser Leu Asn Met Pro Arg Ser Thr Tyr Glu Asn  
 645 650 655  
 Ala Met Lys Glu Val Lys Ala Asp Leu Asn Arg Val Lys Asp Ala Arg  
 660 665 670  
 Glu Asn Asp Phe Asp Glu Lys Leu Arg Ala Glu Leu Glu Asp Glu Ile  
 675 680 685  
 Val Arg Tyr Arg Arg Gln Gln Leu Ser Asn Leu His Gln Leu Glu Glu  
 690 695 700



93

Gln Leu Asp Asp Glu Asp Val Asn Val Gln Glu Arg Gln Met Asp Thr  
 705 710 715 720  
 Arg His Gly Leu Leu Ser Lys Gln His Glu Met Thr Arg Asp Leu Glu  
 725 730 735  
 Ile Gln His Leu Asn Glu Leu His Ala Met Lys Lys Arg His Leu Glu  
 740 745 750  
 Thr Gln His Glu Ala Glu Ser Ala Ser Gln Asn Glu Tyr Thr Gln Arg  
 755 760 765  
 Gln Gln Asp Glu Leu Arg Lys Lys His Ala Met Gln Ser Arg Gln Gln  
 770 775 780  
 Pro Arg Asp Leu Lys Ile Gln Glu Ala Gln Ile Arg Lys Gln Tyr Arg  
 785 790 795 800  
 Gln Val Val Lys Thr Gln Thr Arg Gln Phe Lys Leu Tyr Leu Thr Gln  
 805 810 815  
 Met Val Gln Val Val Pro Lys Asp Glu Gln Lys Glu Leu Thr Ser Arg  
 820 825 830  
 Leu Lys Gln Asp Gln Met Gln Lys Val Ala Leu Leu Ala Ser Gln Tyr  
 835 840 845  
 Glu Ser Gln Ile Lys Lys Met Val Gln Asp Lys Thr Val Lys Leu Glu  
 850 855 860  
 Ser Trp Gln Glu Asp Glu Gln Arg Val Leu Ser Glu Lys Leu Glu Lys  
 865 870 875 880  
 Glu Leu Glu Glu Leu Ile Ala Tyr Gln Lys Lys Thr Arg Ala Thr Leu  
 885 890 895  
 Glu Glu Gln Ile Lys Lys Glu Arg Thr Ala Leu Glu Glu Arg Ile Gly  
 900 905 910  
 Thr Arg Arg Ala Met Leu Glu Gln Lys Ile Ile Glu Glu Arg Glu Gln  
 915 920 925  
 Met Gly Glu Met Arg Arg Leu Lys Lys Glu Gln Ile Arg Asp Arg His  
 930 935 940  
 Ser Gln Glu Arg His Arg Leu Glu Asn His Phe Val Arg Thr Gly Ser  
 945 950 955 960  
 Thr Ser Arg Ser Ser Gly Gly Ile Ala Pro Gly Val Gly Asn Ser Ser  
 965 970 975  
 Ser Ile Gln Met Ala Met  
 980

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 <211> 842  
 <212> PRT  
 <213> KHS1\_h

<400> 91

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Leu Arg Pro Ala Ala Asp Ile Leu Arg Arg Asn Pro Gln Gln Asp Tyr
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Glu Leu Val Gln Arg Val Gly Ser Gly Thr Tyr Gly Asp Val Tyr Lys
      20              25              30

Ala Arg Asn Val His Thr Gly Glu Leu Ala Ala Val Lys Ile Ile Lys
      35              40              45

Leu Glu Pro Gly Asp Asp Phe Ser Leu Ile Gln Gln Glu Ile Phe Met
 50              55              60

Val Lys Glu Cys Lys His Cys Asn Ile Val Ala Tyr Phe Gly Ser Tyr
 65              70              75              80

Leu Ser Arg Glu Lys Leu Trp Ile Cys Met Glu Tyr Cys Gly Gly Gly
      85              90              95

Ser Leu Gln Asp Ile Tyr His Val Thr Gly Pro Leu Ser Glu Leu Gln
 100              105              110

Ile Ala Tyr Val Cys Arg Glu Thr Leu Gln Gly Leu Ala Tyr Leu His
 115              120              125

Thr Lys Gly Lys Met His Arg Asp Ile Lys Gly Ala Asn Ile Leu Leu
 130              135              140

Thr Asp His Gly Asp Val Lys Leu Ala Asp Phe Gly Val Ala Ala Lys
 145              150              155              160

Ile Thr Ala Thr Ile Ala Lys Arg Lys Ser Phe Ile Gly Thr Pro Tyr
      165              170              175

Trp Met Ala Pro Glu Val Ala Ala Val Glu Lys Asn Gly Gly Tyr Asn
      180              185              190

Gln Leu Cys Asp Ile Trp Ala Val Gly Ile Thr Ala Ile Glu Leu Gly
 195              200              205

Glu Leu Gln Pro Pro Met Phe Asp Leu His Pro Met Arg Ala Leu Phe
 210              215              220

Leu Met Ser Lys Ser Asn Phe Gln Pro Pro Lys Leu Lys Asp Lys Thr
 225              230              235              240

Lys Trp Ser Ser Thr Phe His Asn Phe Val Lys Ile Ala Leu Thr Lys
      245              250              255

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Asn Pro Lys Lys Arg Pro Thr Ala Glu Arg Leu Leu Thr His Thr Phe  
 260 265 270  
 Val Ala Gln Pro Gly Leu Ser Arg Ala Leu Ala Val Glu Leu Leu Asp  
 275 280 285  
 Lys Val Asn Asn Pro Asp Asn His Ala His Tyr Thr Glu Ala Asp Asp  
 290 295 300  
 Asp Asp Phe Glu Pro His Ala Ile Ile Arg His Thr Ile Arg Ser Thr  
 305 310 315 320  
 Asn Arg Asn Ala Arg Ala Glu Arg Thr Ala Ser Glu Ile Asn Phe Asp  
 325 330 335  
 Lys Leu Gln Phe Glu Pro Pro Leu Arg Lys Glu Thr Glu Ala Arg Asp  
 340 345 350  
 Glu Met Gly Leu Ser Ser Asp Pro Asn Phe Met Leu Gln Trp Asn Pro  
 355 360 365  
 Phe Val Asp Gly Ala Asn Thr Gly Lys Ser Thr Ser Lys Arg Ala Ile  
 370 375 380  
 Pro Pro Pro Leu Pro Pro Lys Pro Arg Ile Ser Ser Tyr Pro Glu Asp  
 385 390 395 400  
 Asn Phe Pro Asp Glu Glu Lys Ala Ser Thr Ile Lys His Cys Pro Asp  
 405 410 415  
 Ser Glu Ser Arg Ala Pro Gln Ile Leu Arg Arg Gln Ser Ser Pro Ser  
 420 425 430  
 Cys Gly Pro Val Ala Glu Thr Ser Ser Ile Gly Asn Gly Asp Gly Ile  
 435 440 445  
 Ser Lys Leu Met Ser Glu Asn Thr Glu Gly Ser Ala Gln Ala Pro Gln  
 450 455 460  
 Leu Pro Arg Lys Asn Asp Lys Arg Asp Phe Pro Lys Pro Ala Ile Asn  
 465 470 475 480  
 Gly Leu Pro Pro Thr Pro Lys Val Leu Met Gly Ala Cys Phe Ser Lys  
 485 490 495  
 Val Phe Asp Gly Cys Pro Leu Lys Ile Asn Cys Ala Thr Ser Trp Ile  
 500 505 510  
 His Pro Asp Thr Lys Asp Gln Tyr Ile Ile Phe Gly Thr Glu Asp Gly  
 515 520 525  
 Ile Tyr Thr Leu Asn Leu Asn Glu Leu His Glu Ala Thr Met Glu Gln  
 530 535 540

Leu Phe Pro Arg Lys Cys Thr Trp Leu Tyr Val Ile Asn Asn Thr Leu  
 545 550 555 560  
 Met Ser Leu Ser Glu Gly Lys Thr Phe Gln Leu Tyr Ser His Asn Leu  
 565 570 575  
 Ile Ala Leu Phe Glu His Ala Lys Lys Pro Gly Leu Ala Ala His Ile  
 580 585 590  
 Gln Thr His Arg Phe Pro Asp Arg Ile Leu Pro Arg Lys Phe Ala Leu  
 595 600 605  
 Thr Thr Lys Ile Pro Asp Thr Lys Gly Cys His Lys Cys Cys Ile Val  
 610 615 620  
 Arg Asn Pro Tyr Thr Gly His Lys Tyr Leu Cys Gly Ala Leu Gln Ser  
 625 630 635 640  
 Gly Ile Val Leu Leu Gln Trp Tyr Glu Pro Met Gln Lys Phe Met Leu  
 645 650 655  
 Ile Lys His Phe Asp Phe Pro Leu Pro Ser Pro Leu Asn Val Phe Glu  
 660 665 670  
 Met Leu Val Ile Pro Glu Gln Glu Tyr Pro Met Val Cys Val Ala Ile  
 675 680 685  
 Ser Lys Gly Thr Glu Ser Asn Gln Val Val Gln Phe Glu Thr Ile Asn  
 690 695 700  
 Leu Asn Ser Ala Ser Ser Trp Phe Thr Glu Ile Gly Ala Gly Ser Gln  
 705 710 715 720  
 Gln Leu Asp Ser Ile His Val Thr Gln Leu Glu Arg Asp Thr Val Leu  
 725 730 735  
 Val Cys Leu Asp Lys Phe Val Lys Ile Val Asn Leu Gln Gly Lys Leu  
 740 745 750  
 Lys Ser Ser Lys Lys Leu Ala Ser Glu Leu Ser Phe Asp Phe Arg Ile  
 755 760 765  
 Glu Ser Val Val Cys Leu Gln Asp Ser Val Leu Ala Phe Trp Lys His  
 770 775 780  
 Gly Met Gln Gly Lys Ser Phe Lys Ser Asp Glu Val Thr Gln Glu Ile  
 785 790 795 800  
 Ser Asp Glu Thr Arg Val Phe Arg Leu Leu Gly Ser Asp Arg Val Val  
 805 810 815  
 Val Leu Glu Ser Arg Pro Thr Glu Asn Pro Thr Ala His Ser Asn Leu  
 820 825 830  
 Tyr Ile Leu Ala Gly His Glu Asn Ser Tyr

835

840

<210> 92  
 <211> 911  
 <212> PRT  
 <213> LOK\_m

&lt;400&gt; 92

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Met Ala Phe Ala Asn Phe Arg Arg Ile Leu Arg Leu Ser Thr Phe Glu
 1              5              10              15

Lys Arg Lys Ser Arg Glu Tyr Glu His Val Arg Arg Asp Leu Asp Pro
 20              25              30

Asn Asp Val Trp Glu Ile Val Gly Glu Leu Gly Asp Gly Ala Phe Gly
 35              40              45

Lys Val Tyr Lys Ala Lys Asn Lys Glu Thr Gly Ala Leu Ala Ala Ala
 50              55              60

Lys Val Ile Glu Thr Lys Ser Glu Glu Glu Leu Glu Asp Tyr Ile Val
 65              70              75              80

Glu Ile Glu Ile Leu Ala Thr Cys Asp His Pro Tyr Ile Val Lys Leu
 85              90              95

Leu Gly Ala Tyr Tyr Tyr Asp Gly Lys Leu Trp Ile Met Ile Glu Phe
 100             105             110

Cys Pro Gly Gly Ala Val Asp Ala Ile Met Leu Glu Leu Asp Arg Gly
 115             120             125

Leu Thr Glu Pro Gln Ile Gln Val Val Cys Arg Gln Met Leu Glu Ala
 130             135             140

Leu Asn Phe Leu His Gly Lys Arg Ile Ile His Arg Asp Leu Lys Ala
 145             150             155             160

Gly Asn Val Leu Met Thr Leu Glu Gly Asp Ile Arg Leu Ala Asp Phe
 165             170             175

Gly Val Ser Ala Lys Asn Leu Lys Thr Leu Gln Lys Arg Asp Ser Phe
 180             185             190

Ile Gly Thr Pro Tyr Trp Met Ala Pro Glu Val Val Leu Cys Glu Thr
 195             200             205

Met Lys Asp Ala Pro Tyr Asp Tyr Lys Ala Asp Ile Trp Ser Leu Gly
 210             215             220

Ile Thr Leu Ile Glu Met Ala Gln Ile Glu Pro Pro His His Glu Leu
 225             230             235             240

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Asn Pro Met Arg Val Leu Leu Lys Ile Ala Lys Ser Asp Pro Pro Thr  
 245 250 255  
 Leu Leu Thr Pro Ser Lys Trp Ser Val Glu Phe Arg Asp Phe Leu Lys  
 260 265 270  
 Ile Ala Leu Asp Lys Asn Pro Glu Thr Arg Pro Ser Ala Ala Gln Leu  
 275 280 285  
 Leu Gln His Pro Phe Val Ser Arg Val Thr Ser Asn Lys Ala Leu Arg  
 290 295 300  
 Glu Leu Val Ala Glu Ala Lys Ala Glu Val Met Glu Glu Ile Glu Asp  
 305 310 315 320  
 Gly Arg Glu Asp Gly Glu Glu Glu Asp Ala Val Asp Ala Val Pro Pro  
 325 330 335  
 Leu Val Asn His Thr Gln Asp Ser Ala Asn Val Thr Gln Pro Ser Leu  
 340 345 350  
 Asp Ser Asn Lys Leu Leu Gln Asp Ser Ser Thr Pro Leu Pro Pro Ser  
 355 360 365  
 Gln Pro Gln Glu Pro Val Asn Gly Pro Cys Ser Gln Pro Ser Gly Asp  
 370 375 380  
 Gly Pro Leu Gln Thr Thr Ser Pro Ala Asp Gly Leu Ser Lys Asn Asp  
 385 390 395 400  
 Asn Asp Leu Lys Val Pro Val Pro Leu Arg Lys Ser Arg Pro Leu Ser  
 405 410 415  
 Met Asp Ala Arg Ile Gln Met Asp Glu Glu Lys Gln Ile Pro Asp Gln  
 420 425 430  
 Asp Glu Asn Pro Ser Pro Ala Ala Ser Lys Ser Gln Lys Ala Asn Gln  
 435 440 445  
 Ser Arg Pro Asn Ser Ser Ala Leu Glu Thr Leu Gly Gly Glu Ala Leu  
 450 455 460  
 Thr Asn Gly Gly Leu Glu Leu Pro Ser Ser Val Thr Pro Ser His Ser  
 465 470 475 480  
 Lys Arg Ala Ser Asp Cys Ser Asn Leu Ser Thr Ser Glu Ser Met Asp  
 485 490 495  
 Tyr Gly Thr Ser Leu Ser Ala Asp Leu Ser Leu Asn Lys Glu Thr Gly  
 500 505 510  
 Ser Leu Ser Leu Lys Gly Ser Lys Leu His Asn Lys Thr Leu Lys Arg  
 515 520 525

Thr Arg Arg Phe Val Val Asp Gly Val Glu Val Ser Ile Thr Thr Ser  
 530 535 540  
 Lys Ile Ile Ser Glu Asp Glu Lys Lys Asp Glu Glu Met Arg Phe Leu  
 545 550 555 560  
 Arg Arg Gln Glu Leu Arg Glu Leu Arg Leu Leu Gln Lys Glu Glu His  
 565 570 575  
 Arg Asn Gln Thr Gln Leu Ser Ser Lys His Glu Leu Gln Leu Glu Gln  
 580 585 590  
 Met His Lys Arg Phe Glu Gln Glu Ile Asn Ala Lys Lys Lys Phe Tyr  
 595 600 605  
 Asp Val Glu Leu Glu Asn Leu Glu Arg Gln Gln Lys Gln Gln Val Glu  
 610 615 620  
 Lys Met Glu Gln Asp His Ser Val Arg Arg Lys Glu Glu Ala Lys Arg  
 625 630 635 640  
 Ile Arg Leu Glu Gln Asp Arg Asp Tyr Ala Lys Phe Gln Glu Gln Leu  
 645 650 655  
 Lys Gln Met Lys Lys Glu Val Lys Ser Glu Val Glu Lys Leu Pro Arg  
 660 665 670  
 Gln Gln Arg Lys Glu Ser Met Lys Gln Lys Met Glu Glu His Ser Gln  
 675 680 685  
 Lys Lys Gln Arg Leu Asp Arg Asp Phe Val Ala Lys Gln Lys Glu Asp  
 690 695 700  
 Leu Glu Leu Ala Met Arg Lys Leu Thr Thr Glu Asn Arg Arg Glu Ile  
 705 710 715 720  
 Cys Asp Lys Glu Arg Asp Cys Leu Ser Lys Lys Gln Glu Leu Leu Arg  
 725 730 735  
 Asp Arg Glu Ala Ala Leu Trp Glu Met Glu Glu His Gln Leu Gln Glu  
 740 745 750  
 Arg His Gln Leu Val Lys Gln Gln Leu Lys Asp Gln Tyr Phe Leu Gln  
 755 760 765  
 Arg His Asp Leu Leu Arg Lys His Glu Lys Glu Arg Glu Gln Met Gln  
 770 775 780  
 Arg Tyr Asn Gln Arg Met Met Glu Gln Leu Lys Val Arg Gln Gln Gln  
 785 790 795 800  
 Glu Lys Ala Arg Leu Pro Lys Ile Gln Arg Ser Asp Gly Glu Thr Arg  
 805 810 815  
 Met Ala Met Tyr Lys Lys Ser Leu His Ile Asn Gly Ala Gly Ser Ala

100

820                      825                      830  
 Ser Glu Gln Arg Glu Lys Ile Lys Gln Phe Ser Gln Gln Glu Glu Lys  
       835                      840                      845  
 Arg Gln Lys Ala Glu Arg Leu Gln Gln Gln Gln Lys His Glu His Gln  
       850                      855                      860  
 Met Arg Asp Met Val Ala Gln Cys Glu Ser Asn Met Ser Glu Leu Gln  
       865                      870                      875                      880  
 Gln Leu Gln Asn Glu Lys Cys Tyr Leu Leu Val Glu His Glu Thr Gln  
                              885                      890                      895  
 Lys Leu Lys Ala Leu Asp Glu Ser His Asn Gln Ser Leu Lys Glu  
                              900                      905                      910

<210> 93  
 <211> 545  
 <212> PRT  
 <213> PAK1\_h

<400> 93

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                               20                              25                              30  
 Thr Leu Asn His Gly Ser Lys Pro Leu Pro Pro Asn Pro Glu Glu Lys  
                               35                              40                              45  
 Lys Lys Lys Asp Arg Phe Tyr Arg Ser Ile Leu Pro Gly Asp Lys Thr  
                               50                              55                              60  
 Asn Lys Lys Lys Glu Lys Glu Arg Pro Glu Ile Ser Leu Pro Ser Asp  
   65                              70                              75                              80  
 Phe Glu His Thr Ile His Val Gly Phe Asp Ala Val Thr Gly Glu Phe  
                               85                              90                              95  
 Thr Gly Met Pro Glu Gln Trp Ala Arg Leu Leu Gln Thr Ser Asn Ile  
                               100                              105                              110  
 Thr Lys Ser Glu Gln Lys Lys Asn Pro Gln Ala Val Leu Asp Val Leu  
                               115                              120                              125  
 Glu Phe Tyr Asn Ser Lys Lys Thr Ser Asn Ser Gln Lys Tyr Met Ser  
   130                              135                              140



101

Phe Thr Asp Lys Ser Ala Glu Asp Tyr Asn Ser Ser Asn Ala Leu Asn  
 145 150 155 160  
 Val Lys Ala Val Ser Glu Thr Pro Ala Val Pro Pro Val Ser Glu Asp  
 165 170 175  
 Glu Asp Asp Asp Asp Asp Ala Thr Pro Pro Pro Val Ile Ala Pro  
 180 185 190  
 Arg Pro Glu His Thr Lys Ser Val Tyr Thr Arg Ser Val Ile Glu Pro  
 195 200 205  
 Leu Pro Val Thr Pro Thr Arg Asp Val Ala Thr Ser Pro Ile Ser Pro  
 210 215 220  
 Thr Glu Asn Asn Thr Thr Pro Pro Asp Ala Leu Thr Leu Asn Thr Glu  
 225 230 235 240  
 Lys Gln Lys Lys Lys Pro Lys Met Ser Asp Glu Glu Ile Leu Glu Lys  
 245 250 255  
 Leu Arg Ser Ile Val Ser Val Gly Asp Pro Lys Lys Lys Tyr Thr Arg  
 260 265 270  
 Phe Glu Lys Ile Gly Gln Gly Ala Ser Gly Thr Val Tyr Thr Ala Met  
 275 280 285  
 Asp Val Ala Thr Gly Gln Glu Val Ala Ile Lys Gln Met Asn Leu Gln  
 290 295 300  
 Gln Gln Pro Lys Lys Glu Leu Ile Ile Asn Glu Ile Leu Val Met Arg  
 305 310 315 320  
 Glu Asn Lys Asn Pro Asn Ile Val Asn Tyr Leu Asp Ser Tyr Leu Val  
 325 330 335  
 Gly Asp Glu Leu Trp Val Val Met Glu Tyr Leu Ala Gly Gly Ser Leu  
 340 345 350  
 Thr Asp Val Val Thr Glu Thr Cys Met Asp Glu Gly Gln Ile Ala Ala  
 355 360 365  
 Val Cys Arg Glu Cys Leu Gln Ala Leu Glu Ser Leu His Ser Asn Gln  
 370 375 380  
 Val Ile His Arg Asp Ile Lys Ser Asp Asn Ile Leu Leu Gly Met Asp  
 385 390 395 400  
 Gly Ser Val Lys Leu Thr Asp Phe Gly Phe Cys Ala Gln Ile Thr Pro  
 405 410 415  
 Glu Gln Ser Lys Arg Ser Thr Met Val Gly Thr Pro Tyr Trp Met Ala  
 420 425 430  
 Pro Glu Val Val Thr Arg Lys Ala Tyr Gly Pro Lys Val Asp Ile Trp  
 435 440 445

102

Ser Leu Gly Ile Met Ala Ile Glu Met Ile Glu Gly Glu Pro Pro Tyr  
 450 455 460  
 Leu Asn Glu Asn Pro Leu Arg Ala Leu Tyr Leu Ile Ala Thr Asn Gly  
 465 470 475 480  
 Thr Pro Glu Leu Gln Asn Pro Glu Lys Leu Ser Ala Ile Phe Arg Asp  
 485 490 495  
 Phe Leu Asn Arg Cys Leu Glu Met Asp Val Glu Lys Arg Gly Ser Ala  
 500 505 510  
 Lys Glu Leu Leu Gln His Gln Phe Leu Lys Ile Ala Lys Pro Leu Ser  
 515 520 525  
 Ser Leu Thr Pro Leu Ile Ala Ala Ala Lys Glu Ala Thr Lys Asn Asn  
 530 535 540

His  
545

<210> 94  
 <211> 506  
 <212> PRT  
 <213> PAK65\_h

<400> 94

Met Glu Glu Thr Gln Gln Lys Ser Asn Leu Glu Leu Leu Ser Ala Asn  
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 His Lys Ile Ile Ser Ile Phe Ser Gly Thr Glu Lys Gly Ser Lys Lys  
 35 40 45  
 Lys Glu Lys Glu Arg Pro Glu Ile Ser Pro Pro Ser Asp Phe Glu His  
 50 55 60  
 Thr Ile His Val Gly Phe Asp Thr Val Thr Gly Glu Phe Thr Gly Met  
 65 70 75 80  
 Pro Glu Gln Trp Ala Arg Leu Leu Gln Thr Ser Asn Ile Thr Lys Leu  
 85 90 95  
 Glu Gln Lys Lys Asn Pro Gln Ala Val Leu Asp Val Leu Lys Phe Tyr  
 100 105 110  
 Asp Ser Asn Thr Val Lys Gln Lys Tyr Leu Ser Phe Thr Pro Pro Glu  
 115 120 125

103

Lys Asp Gly Phe Pro Ser Gly Thr Pro Ala Leu Asn Ala Lys Gly Thr  
 130 135 140  
 Glu Ala Pro Ala Val Val Thr Glu Glu Glu Asp Asp Glu Glu Thr  
 145 150 155 160  
 Ala Pro Pro Val Ile Ala Pro Arg Pro Asp His Thr Lys Ser Ile Tyr  
 165 170 175  
 Thr Arg Ser Val Ile Asp Pro Val Pro Ala Pro Val Gly Asp Ser His  
 180 185 190  
 Val Asp Gly Ala Ala Lys Ser Leu Asp Lys Gln Lys Lys Lys Thr Lys  
 195 200 205  
 Met Thr Asp Glu Glu Ile Met Glu Lys Leu Arg Thr Ile Val Ser Ile  
 210 215 220  
 Gly Asp Pro Lys Lys Lys Tyr Thr Arg Tyr Glu Lys Ile Gly Gln Gly  
 225 230 235 240  
 Ala Ser Gly Thr Val Phe Thr Ala Thr Asp Val Ala Leu Gly Gln Glu  
 245 250 255  
 Val Ala Ile Lys Gln Ile Asn Leu Gln Lys Gln Pro Lys Lys Glu Leu  
 260 265 270  
 Ile Ile Asn Glu Ile Leu Val Met Lys Glu Leu Lys Asn Pro Asn Ile  
 275 280 285  
 Val Asn Phe Leu Asp Ser Tyr Leu Val Gly Asp Glu Leu Phe Val Val  
 290 295 300  
 Met Glu Tyr Leu Ala Gly Arg Ser Leu Thr Asp Val Val Thr Glu Thr  
 305 310 315 320  
 Cys Met Asp Glu Ala Gln Ile Ala Ala Val Cys Arg Glu Cys Leu Gln  
 325 330 335  
 Ala Leu Glu Phe Leu His Ala Asn Gln Val Ile His Arg Asp Ile Lys  
 340 345 350  
 Ser Asp Asn Val Leu Leu Gly Met Glu Gly Ser Val Lys Leu Thr Asp  
 355 360 365  
 Phe Gly Phe Cys Ala Gln Ile Thr Pro Glu Gln Ser Lys Arg Ser Thr  
 370 375 380  
 Met Val Gly Thr Pro Tyr Trp Met Ala Pro Glu Val Val Thr Arg Lys  
 385 390 395 400  
 Ala Tyr Gly Pro Lys Val Asp Ile Trp Ser Leu Gly Ile Met Ala Ile  
 405 410 415  
 Glu Met Val Glu Gly Glu Pro Pro Tyr Leu Asn Glu Asn Pro Leu Arg

430

Lys Ser Ala His Gly Tyr Ile Ala Ala His Gln Ser Asn Thr Lys Thr  
145                      150                      155                      160

105

Gly Ser Glu Pro Pro Leu Ala Pro Pro Val Ser Glu Glu Glu Asp Glu  
 165 170 175  
 Glu Glu Glu Glu Glu Glu Asp Asp Asn Glu Pro Pro Pro Val Ile Ala  
 180 185 190  
 Pro Arg Pro Glu His Thr Lys Ser Ile Tyr Thr Arg Ser Val Val Glu  
 195 200 205  
 Ser Ile Ala Ser Pro Ala Ala Pro Asn Lys Glu Asp Ile Pro Pro Ser  
 210 215 220  
 Ala Glu Asn Ala Asn Ser Thr Thr Leu Tyr Arg Asn Thr Asp Arg Gln  
 225 230 235 240  
 Arg Lys Lys Ser Lys Met Thr Asp Glu Glu Ile Leu Glu Lys Leu Arg  
 245 250 255  
 Ser Ile Val Ser Val Gly Asp Pro Lys Lys Lys Tyr Thr Arg Leu Glu  
 260 265 270  
 Lys Ile Gly Gln Gly Ala Ser Gly Thr Val Tyr Thr Ala Leu Asp Ile  
 275 280 285  
 Ala Thr Gly Gln Glu Val Ala Ile Lys Gln Met Asn Leu Gln Gln Gln  
 290 295 300  
 Pro Lys Lys Glu Leu Ile Ile Asn Glu Ile Leu Val Met Arg Glu Asn  
 305 310 315 320  
 Lys Asn Pro Asn Ile Val Asn Tyr Leu Asp Ser Tyr Leu Val Gly Asp  
 325 330 335  
 Glu Leu Trp Val Val Met Glu Tyr Leu Ala Gly Gly Ser Leu Thr Asp  
 340 345 350  
 Val Val Thr Glu Thr Cys Met Asp Val Gly Gln Ile Ala Ala Val Cys  
 355 360 365  
 Arg Glu Cys Leu Gln Ala Leu Asp Phe Leu His Ser Asn Gln Val Ile  
 370 375 380  
 His Arg Asp Ile Lys Ser Asp Asn Ile Leu Leu Gly Met Asp Gly Ser  
 385 390 395 400  
 Val Lys Leu Thr Asp Phe Gly Phe Cys Ala Gln Ile Thr Pro Glu Gln  
 405 410 415  
 Ser Lys Arg Ser Thr Met Val Gly Thr Pro Tyr Trp Met Ala Pro Glu  
 420 425 430  
 Val Val Thr Arg Lys Ala Tyr Gly Pro Lys Val Asp Ile Trp Ser Leu  
 435 440 445  
 Gly Ile Met Ala Ile Glu Met Val Glu Gly Glu Pro Pro Tyr Leu Asn

106

450                      455                      460  
 Glu Asn Pro Leu Arg Ala Leu Tyr Leu Ile Ala Thr Asn Gly Thr Pro  
 465                      470                      475                      480  
 Glu Leu Gln Asn Pro Glu Arg Leu Ser Ala Val Phe His Asp Phe Leu  
 485                      490                      495  
 Asn Arg Cys Leu Glu Met Asp Val Asp Arg Arg Gly Ser Ala Lys Glu  
 500                      505                      510  
 Leu Leu Gln His Pro Phe Leu Lys Leu Ala Lys Pro Leu Ser Ser Leu  
 515                      520                      525  
 Thr Pro Leu Ile Ile Ala Ala Lys Glu Ala Ile Lys Asn Ser Ser Arg  
 530                      535                      540

<400> 96  
 <210> 96  
 <211> 2110  
 <212> DNA  
 <213> Full Length Mammalian (Human) STLK5

<400> 96

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 cgggtgggtct cggaaaagt cattgttgag ggcttaagag atttggaact atttgagagac 180  
 caatgatgcg agctcagagt caatagcatc cttctctaaa caggaggtca tgagtagctt 240  
 tctgccagag ggagggtgtt acgagctgct cactgtgata ggcaaaggat ttgaggacct 300  
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 taacctagaa gcttgttcca atgagatggt aacattcttg cagggcgagc tgcattgtctc 420  
 caaactcttc aaccatccca atatcgtgcc atatcgagcc acttttattg cagacaatga 480  
 gctgtgggtt gtcacatcat tcatggcata cggttctgca aaagatctca tctgtacaca 540  
 cttcatggat ggcataaatg agctggcgat tgcttacatc ctgcaggggg tgctgaaggc 600  
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 gggcagattg ggtagaaagg acattcttcc aggaagttg actgctgact gattgggaaa 1500  
 gaaaatcctg gagagatact tcactgctcc aaggcttttg agacacaagg gaatctcaac 1560  
 aaccagggat caggagggtc caaagccgac attccagtc ctgtgagctc aggtgacctc 1620

107

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ctccgcagaa gagagatgct gctctggccc tgggagctga attccaagcc cagggttttg 1680
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aactttgctc tcagatgcct cagatgctat aggtcagtga aagggaagt agtaagctgc 1800
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taagcacaga ctaaggctgg aacagtccat ccttatccct cttctggctt gggccctgac 1920
acctaagtct tttccacggt ttatgtgtgt gcctcattcc tttccacca agaatccatc 1980
ttagcgctc ctgccagctg ccctggtgct ttctccaagg gccatcagtg tcttgccatg 2040
cttgagggtc taagtcctta tgctgtgtta gtttcgttgt cagaacaaat taaaattttc 2100
agagacgctg                                     2110

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<210> 97
<211> 373
<212> PRT
<213> Full Length Mammalian (Human) STLK 5

<400> 97

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Met Ser Ser Phe Leu Pro Glu Gly Gly Cys Tyr Glu Leu Leu Thr Val
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Ile Gly Lys Gly Phe Glu Asp Leu Met Thr Val Asn Leu Ala Arg Tyr
      20             25             30

Lys Pro Thr Gly Glu Tyr Val Thr Val Arg Arg Ile Asn Leu Glu Ala
      35             40             45

Cys Ser Asn Glu Met Val Thr Phe Leu Gln Gly Glu Leu His Val Ser
 50             55             60

Lys Leu Phe Asn His Pro Asn Ile Val Pro Tyr Arg Ala Thr Phe Ile
 65             70             75             80

Ala Asp Asn Glu Leu Trp Val Val Thr Ser Phe Met Ala Tyr Gly Ser
      85             90             95

Ala Lys Asp Leu Ile Cys Thr His Phe Met Asp Gly Met Asn Glu Leu
      100            105            110

Ala Ile Ala Tyr Ile Leu Gln Gly Val Leu Lys Ala Leu Asp Tyr Ile
      115            120            125

His His Met Gly Tyr Val His Arg Ser Val Lys Ala Ser His Ile Leu
      130            135            140

Ile Ser Val Asp Gly Lys Val Tyr Leu Ser Gly Leu Arg Ser Asn Leu
      145            150            155            160

Ser Met Ile Ser His Gly Gln Arg Gln Arg Val Val His Asp Phe Pro
      165            170            175

Lys Tyr Ser Val Lys Val Leu Pro Trp Leu Ser Pro Glu Val Leu Gln
      180            185            190

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Gln Asn Leu Gln Gly Tyr Asp Ala Lys Ser Asp Ile Tyr Ser Val Gly  
 195 200 205  
 Ile Thr Ala Cys Glu Leu Ala Asn Gly His Val Pro Phe Lys Asp Met  
 210 215 220  
 Pro Ala Thr Gln Met Leu Leu Glu Lys Leu Asn Gly Thr Val Pro Cys  
 225 230 235 240  
 Leu Leu Asp Thr Ser Thr Ile Pro Ala Glu Glu Leu Thr Met Ser Pro  
 245 250 255  
 Ser Arg Ser Val Ala Asn Ser Gly Leu Ser Asp Ser Leu Thr Thr Ser  
 260 265 270  
 Thr Pro Arg Pro Ser Asn Gly Asp Ser Pro Ser His Pro Tyr His Arg  
 275 280 285  
 Thr Phe Ser Pro His Phe His His Phe Val Glu Gln Cys Leu Gln Arg  
 290 295 300  
 Asn Pro Asp Ala Arg Pro Ser Ala Ser Thr Leu Leu Asn His Ser Phe  
 305 310 315 320  
 Phe Lys Gln Ile Lys Arg Arg Ala Ser Glu Ala Leu Pro Glu Leu Leu  
 325 330 335  
 Arg Pro Val Thr Pro Ile Thr Asn Phe Glu Gly Ser Gln Ser Gln Asp  
 340 345 350  
 His Ser Gly Ile Phe Gly Leu Val Thr Asn Leu Glu Glu Leu Glu Val  
 355 360 365  
 Asp Asp Trp Glu Phe  
 370

<210> 98  
 <211> 2001  
 <212> DNA  
 <213> Mammalian (Human) STLK6

<400> 98

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 cactcagacc tgaaaaacag tctgaaacca gtatccatca atacttggtt gatgagccaa  
 ccttttctg gtcacgtcca tccactagag ccagtgaagt actatgttcc accaacgttt 240  
 ctactatga gctccaagta gaaataggaa gaggatttga caacttgact tctgtccatc 300  
 ttgcacggca tactccacg ggaacactgg taactataaa aattacaaat ctggaaaact 360  
 gcaatgaaga acgctgaaa gctttacaga aagccgtgat tctatccac tttttccggc 420



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atcccaatat tacaacttat tggacagttt tcactgttgg cagctggcctt tgggttattt 480
ctccatttat ggcctatggt tcagcaagtc aactcttgag gacctatttt cctgaaggaa 540
tgagtgaaac ttttaataaga aacattctct ttggagccgt gagagggttg aactatctgc 600
accaaaatgg ctgtattcac aggagtatta aagccagcca tatcctcatt tctggtgatg 660
gcctagtgac cctctctggc ctttcccatc tgcatagttt ggttaagcat ggacagaggc 720
atagggctgt gtatgatttc ccacagttca gcacatcagt gcagccgtgg ctgagtccag 780
aactactgag acaggattta catgggtata atgtgaagtc agatatttac agtgttggga 840
ttacagcatg tgaattagcc agtgggcagg tgccctttcca ggacatgcat agaactcaga 900
tgctgttaca gaaactgaaa ggtcctcctt atagcccatt ggatatcagt attttccctc 960
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<210> 99  
 <211> 373  
 <212> PRT  
 <213> Mammalian (Human) STLK6

<400> 99

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Met Ser Ser Phe Leu Pro Glu Gly Gly Cys Tyr Glu Leu Leu Thr Val
 1             5             10             15

Ile Gly Lys Gly Phe Glu Asp Leu Met Thr Val Asn Leu Ala Arg Tyr
      20             25             30

Lys Pro Thr Gly Glu Tyr Val Thr Val Arg Arg Ile Asn Leu Glu Ala
      35             40             45

Cys Ser Asn Glu Met Val Thr Phe Leu Gln Gly Glu Leu His Val Ser
      50             55             60

Lys Leu Phe Asn His Pro Asn Ile Val Pro Tyr Arg Ala Thr Phe Ile
      65             70             75             80

Ala Asp Asn Glu Leu Trp Val Val Thr Ser Phe Met Ala Tyr Gly Ser
      85             90             95

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110

Ala Lys Asp Leu Ile Cys Thr His Phe Met Asp Gly Met Asn Glu Leu  
100 105 110

Ala Ile Ala Tyr Ile Leu Gln Gly Val Leu Lys Ala Leu Asp Tyr Ile  
115 120 125

His His Met Gly Tyr Val His Arg Ser Val Lys Ala Ser His Ile Leu  
130 135 140

Ile Ser Val Asp Gly Lys Val Tyr Leu Ser Gly Leu Arg Ser Asn Leu  
145 150 155 160

Ser Met Ile Ser His Gly Gln Arg Gln Arg Val Val His Asp Phe Pro  
165 170 175

Lys Tyr Ser Val Lys Val Leu Pro Trp Leu Ser Pro Glu Val Leu Gln  
180 185 190

Gln Asn Leu Gln Gly Tyr Asp Ala Lys Ser Asp Ile Tyr Ser Val  
195 200 205

Ile Thr Ala Cys Glu Leu Ala Asn Gly His Val Pro Phe Lys Asp Met  
210 215 220

Pro Ala Thr Gln Met Leu Leu Glu Lys Leu Asn Gly Thr Val Pro  
225 230 235 240

Leu Leu Asp Thr Ser Thr Ile Pro Ala Glu Glu Leu Thr Met Ser Pro  
245 250 255

Ser Arg Ser Val Ala Asn Ser Gly Leu Ser Asp Ser Leu Thr Thr  
260 265 270

Thr Pro Arg Pro Ser Asn Gly Asp Ser Pro Ser His Pro Tyr His Arg  
275 280 285

Thr Phe Ser Pro His Phe His His Phe Val Glu Gln Cys Leu Gln  
290 295 300

Asn Pro Asp Ala Arg Pro Ser Ala Ser Thr Leu Leu Asn His Ser Phe  
305 310 315 320

Phe Lys Gln Ile Lys Arg Arg Ala Ser Glu Ala Leu Pro Glu Leu  
325 330 335

Arg Pro Val Thr Pro Ile Thr Asn Phe Glu Gly Ser Gln Ser Gln Asp  
340 345 350

His Ser Gly Ile Phe Gly Leu Val Thr Asn Leu Glu Glu Leu Glu  
355 360 365

Asp Asp Trp Glu Phe

370

111

<210> 100  
 <211> 311  
 <212> DNA  
 <213> Mammalian (Human) STLK7

<400> 100

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aatgtcaaac tagcatggat gaactcctga aagaaattca agccatgagt caatgccatc 180
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aacacaaaag t 311
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<210> 101  
 <211> 103  
 <212> PRT  
 <213> Mammalian (Human) STLK7

<400> 101

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Asn Arg Asp Asp Tyr Glu Leu Gln Glu Val Ile Gly Ser Gly Ala Thr
 1             5             10             15

Ala Val Val Gln Ala Ala Tyr Cys Ala Pro Lys Lys Glu Lys Val Ala
      20             25             30

Ile Lys Arg Ile Asn Leu Glu Lys Cys Gln Thr Ser Met Asp Glu Leu
      35             40             45

Leu Lys Glu Ile Gln Ala Met Ser Gln Cys His His Pro Asn Ile Val
      50             55             60

Ser Tyr Tyr Thr Ser Phe Val Val Lys Asp Glu Leu Trp Leu Val Met
      65             70             75             80

Lys Leu Leu Ser Gly Gly Ser Val Leu Asp Ile Ile Lys His Ile Val
      85             90             95

Ala Lys Gly Glu His Lys Ser
      100
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<210> 102  
 <211> 2806

&lt;212&gt; DNA

&lt;213&gt; Full Length Mammalian (Human) PAK5

&lt;400&gt; 102

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<210> 103  
 <211> 591  
 <212> PRT  
 <213> Full Length Mammalian (Human) PAK5hu

<400> 103

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Met Phe Gly Lys Arg Lys Lys Arg Val Glu Ile Ser Ala Pro Ser Asn
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Phe Glu His Arg Val His Thr Gly Phe Asp Gln His Glu Gln Lys Phe
      20             25             30

Thr Gly Leu Pro Arg Gln Trp Gln Ser Leu Ile Glu Glu Ser Ala Arg
      35             40             45

Arg Pro Lys Pro Leu Val Asp Pro Ala Cys Ile Thr Ser Ile Gln Pro
      50             55             60

Gly Ala Pro Lys Thr Ile Val Arg Gly Ser Lys Gly Ala Lys Asp Gly
65             70             75             80

Ala Leu Thr Leu Leu Leu Asp Glu Phe Glu Asn Met Ser Val Thr Arg
      85             90             95

Ser Asn Ser Leu Arg Arg Asp Ser Pro Pro Pro Pro Ala Arg Ala Arg
      100            105            110

Gln Glu Asn Gly Met Pro Glu Glu Pro Ala Thr Thr Ala Arg Gly Gly
      115            120            125

Pro Gly Lys Ala Gly Ser Arg Gly Arg Phe Ala Gly His Ser Glu Ala
      130            135            140

Gly Gly Gly Ser Gly Asp Arg Arg Arg Ala Gly Pro Glu Lys Arg Pro
      145            150            155            160

Lys Ser Ser Arg Glu Gly Ser Gly Gly Pro Gln Glu Ser Ser Arg Asp
      165            170            175

Lys Arg Pro Leu Ser Gly Pro Asp Val Gly Thr Pro Gln Pro Ala Gly
      180            185            190

Leu Ala Ser Gly Ala Lys Leu Ala Ala Gly Arg Pro Phe Asn Thr Tyr
      195            200            205

Pro Arg Ala Asp Thr Asp His Pro Ser Arg Gly Ala Gln Gly Glu Pro
      210            215            220

His Asp Val Ala Pro Asn Gly Pro Ser Ala Gly Gly Leu Ala Ile Pro
      225            230            235            240

Gln Ser Ser Ser Ser Ser Ser Arg Pro Pro Thr Arg Ala Arg Gly Ala
      245            250            255

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Pro Ser Pro Gly Val Leu Gly Pro His Ala Ser Glu Pro Gln Leu Ala  
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 275 280 285  
 Pro Arg Ser Pro Gln Arg Glu Pro Gln Arg Val Ser His Glu Gln Phe  
 290 295 300  
 Arg Ala Ala Leu Gln Leu Val Val Asp Pro Gly Asp Pro Arg Ser Tyr  
 305 310 315 320  
 Leu Asp Asn Phe Ile Lys Ile Gly Glu Gly Ser Thr Gly Ile Val Cys  
 325 330 335  
 Ile Ala Thr Val Arg Ser Ser Gly Lys Leu Val Ala Val Lys Lys Met  
 340 345 350  
 Asp Leu Arg Lys Gln Gln Arg Arg Glu Leu Leu Phe Asn Glu Val Val  
 355 360 365  
 Ile Met Arg Asp Tyr Gln His Glu Asn Val Val Glu Met Tyr Asn Ser  
 370 375 380  
 Tyr Leu Val Gly Asp Glu Leu Trp Val Val Met Glu Phe Leu Glu Gly  
 385 390 395 400  
 Gly Ala Leu Thr Asp Ile Val Thr His Thr Arg Met Asn Glu Glu Gln  
 405 410 415  
 Ile Ala Ala Val Cys Leu Ala Val Leu Gln Ala Leu Ser Val Leu His  
 420 425 430  
 Ala Gln Gly Val Ile His Arg Asp Ile Lys Ser Asp Ser Ile Leu Leu  
 435 440 445  
 Thr His Asp Gly Arg Val Lys Leu Ser Asp Phe Gly Phe Cys Ala Gln  
 450 455 460  
 Val Ser Lys Glu Val Pro Arg Arg Lys Ser Leu Val Gly Thr Pro Tyr  
 465 470 475 480  
 Trp Met Ala Pro Glu Leu Ile Ser Arg Leu Pro Tyr Gly Pro Glu Val  
 485 490 495  
 Asp Ile Trp Ser Leu Gly Ile Met Val Ile Glu Met Val Asp Gly Glu  
 500 505 510  
 Pro Pro Tyr Phe Asn Glu Pro Pro Leu Lys Ala Met Lys Met Ile Arg  
 515 520 525  
 Asp Asn Leu Pro Pro Arg Leu Lys Asn Leu His Lys Val Ser Pro Ser  
 530 535 540

115

Leu Lys Gly Phe Leu Asp Arg Leu Leu Val Arg Asp Pro Ala Gln Arg  
545 550 555 560

Ala Thr Ala Ala Glu Leu Leu Lys His Pro Phe Leu Ala Lys Ala Gly  
565 570 575

Pro Pro Ala Ser Ile Val Pro Leu Met Arg Gln Asn Arg Thr Arg  
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<210> 104  
<211> 3684  
<212> DNA  
<213> Full Length Mammalian (Human) ZC4

<400> 104

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116

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&lt;210&gt; 105

&lt;211&gt; 1227

&lt;212&gt; PRT

&lt;213&gt; Full Length Mammalian (Human) ZC4

&lt;400&gt; 105

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Met Ala Gly Pro Gly Gly Trp Arg Asp Arg Glu Val Thr Asp Leu Gly
 1             5             10             15

His Leu Pro Asp Pro Thr Gly Ile Phe Ser Leu Asp Lys Thr Ile Gly
      20             25             30

Leu Gly Thr Tyr Gly Arg Ile Tyr Leu Gly Leu His Glu Lys Thr Gly
      35             40             45

Ala Phe Thr Ala Val Lys Val Met Asn Ala Arg Lys Asp Glu Glu Glu
      50             55             60

Asp Leu Arg Thr Glu Leu Asn Leu Leu Arg Lys Tyr Ser Phe His Lys
      65             70             75             80

Asn Ile Val Ser Phe Tyr Gly Ala Phe Phe Lys Leu Ser Pro Pro Gly
      85             90             95

Gln Arg His Gln Leu Trp Met Val Met Glu Leu Cys Ala Ala Gly Ser
      100             105             110

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117

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His Ala His	Arg Val Ile	His Arg Asp	Ile Lys Gly	Gln Asn Val	Leu
145		150		155	160
Leu Thr His	Asn Ala Glu	Val Lys Leu	Val Asp Phe	Gly Val Ser	Ala
	165		170		175
Gln Val Ser	Arg Thr Asn	Gly Arg Arg	Asn Ser Phe	Ile Gly Thr	Pro
	180		185		190
Tyr Trp Met	Ala Pro Glu	Val Ile Asp	Cys Asp Glu	Asp Pro Arg	Arg
195		200		205	
Ser Tyr Asp	Tyr Arg Ser	Asp Val Trp	Ser Val Gly	Ile Thr Ala	Ile
210		215		220	
Glu Met Ala	Glu Gly Ala	Pro Pro Leu	Cys Asn Leu	Gln Pro Leu	Glu
225		230		235	240
Ala Leu Phe	Val Ile Leu	Arg Glu Ser	Ala Pro Thr	Val Lys Ser	Ser
	245		250		255
Gly Trp Ser	Arg Lys Phe	His Asn Phe	Met Glu Lys	Cys Thr Ile	Lys
	260		265		270
Asn Phe Leu	Phe Arg Pro	Thr Ser Ala	Asn Met Leu	Gln His Pro	Phe
275		280		285	
Val Arg Asp	Ile Lys Asn	Glu Arg His	Val Val Glu	Ser Leu Thr	Arg
290		295		300	
His Leu Thr	Gly Ile Ile	Lys Lys Arg	Gln Lys Lys	Glu Gln Ala	Arg
305		310		315	320
Glu Lys Lys	Ser Lys Val	Ser Thr Leu	Arg Gln Ala	Leu Ala Lys	Arg
	325		330		335
Leu Ser Pro	Lys Arg Phe	Arg Ala Lys	Ser Ser Trp	Arg Pro Glu	Lys
	340		345		350
Leu Glu Leu	Ser Asp Leu	Glu Ala Arg	Arg Gln Arg	Arg Gln Arg	Arg
	355		360		365
Trp Glu Asp	Ile Phe Asn	Gln His Glu	Glu Glu Glu	Leu Arg Gln	Val
370		375		380	
Lys Asp Lys	Glu Asp Glu	Ser Ser Asp	Asn Asp Glu	Val Phe His	Ser
385		390		395	400

118

Ile Gln Ala Glu Val Gln Ile Glu Pro Leu Lys Pro Tyr Ile Ser Asn  
 405 410 415  
 Pro Lys Lys Ile Glu Val Gln Glu Arg Ser Pro Ser Val Pro Asn Asn  
 420 425 430  
 Gln Asp His Ala His His Val Lys Phe Ser Ser Ser Val Pro Gln Arg  
 435 440 445  
 Ser Leu Leu Glu Gln Ala Gln Lys Pro Ile Asp Ile Arg Gln Arg Ser  
 450 455 460  
 Ser Gln Asn Arg Gln Asn Trp Leu Ala Ala Ser Gly Asp Ser Lys His  
 465 470 475 480  
 Lys Ile Leu Ala Gly Lys Thr Gln Ser Tyr Cys Leu Thr Ile Tyr Ile  
 485 490 495  
 Ser Glu Val Lys Lys Glu Glu Phe Gln Glu Gly Met Asn Gln Lys Cys  
 500 505 510  
 Gln Gly Ala Gln Val Gly Leu Gly Pro Glu Gly His Cys Ile Trp Gln  
 515 520 525  
 Leu Gly Glu Ser Ser Ser Glu Glu Glu Ser Pro Val Thr Gly Arg Arg  
 530 535 540  
 Ser Gln Ser Ser Pro Pro Tyr Ser Thr Ile Asp Gln Lys Leu Leu Val  
 545 550 555 560  
 Asp Ile His Val Pro Asp Gly Phe Lys Val Gly Lys Ile Ser Pro Pro  
 565 570 575  
 Val Tyr Leu Thr Asn Glu Trp Val Gly Tyr Asn Ala Leu Ser Glu Ile  
 580 585 590  
 Phe Arg Asn Asp Trp Leu Thr Pro Ala Pro Val Ile Gln Pro Pro Glu  
 595 600 605  
 Glu Asp Gly Asp Tyr Val Glu Leu Tyr Asp Ala Ser Ala Asp Thr Asp  
 610 615 620  
 Gly Asp Asp Asp Asp Glu Ser Asn Asp Thr Phe Glu Asp Thr Tyr Asp  
 625 630 635 640  
 His Ala Asn Gly Asn Asp Asp Leu Asp Asn Gln Val Asp Gln Ala Asn  
 645 650 655  
 Asp Val Cys Lys Asp His Asp Asp Asp Asn Asn Lys Phe Val Asp Asp  
 660 665 670  
 Val Asn Asn Asn Tyr Tyr Glu Ala Pro Ser Cys Pro Arg Ala Ser Tyr  
 675 680 685

Gly Arg Asp Gly Ser Cys Lys Gln Asp Gly Tyr Asp Gly Ser Arg Gly  
 690 695 700  
 Lys Glu Glu Ala Tyr Arg Gly Tyr Gly Ser His Thr Ala Asn Arg Ser  
 705 710 715 720  
 His Gly Gly Ser Ala Ala Ser Glu Asp Asn Ala Ala Ile Gly Asp Gln  
 725 730 735  
 Glu Glu His Ala Ala Asn Ile Gly Ser Glu Arg Arg Gly Ser Glu Gly  
 740 745 750  
 Asp Gly Gly Lys Gly Val Val Arg Thr Ser Glu Glu Ser Gly Ala Leu  
 755 760 765  
 Gly Leu Asn Gly Glu Glu Asn Cys Ser Glu Thr Asp Gly Pro Gly Leu  
 770 775 780  
 Lys Arg Pro Ala Ser Gln Asp Phe Glu Tyr Leu Gln Glu Glu Pro Gly  
 785 790 795 800  
 Gly Gly Asn Glu Ala Ser Asn Ala Ile Asp Ser Gly Ala Ala Pro Ser  
 805 810 815  
 Ala Pro Asp His Glu Ser Asp Asn Lys Asp Ile Ser Glu Ser Ser Thr  
 820 825 830  
 Gln Ser Asp Phe Ser Ala Asn His Ser Ser Pro Ser Lys Gly Ser Gly  
 835 840 845  
 Met Ser Ala Asp Ala Asn Phe Ala Ser Ala Ile Leu Tyr Ala Gly Phe  
 850 855 860  
 Val Glu Val Pro Glu Glu Ser Pro Lys Gln Pro Ser Glu Val Asn Val  
 865 870 875 880  
 Asn Pro Leu Tyr Val Ser Pro Ala Cys Lys Lys Pro Leu Ile His Met  
 885 890 895  
 Tyr Glu Lys Glu Phe Thr Ser Glu Ile Cys Cys Gly Ser Leu Trp Gly  
 900 905 910  
 Val Asn Leu Leu Leu Gly Thr Arg Ser Asn Leu Tyr Leu Met Asp Arg  
 915 920 925  
 Ser Gly Lys Ala Asp Ile Thr Lys Leu Ile Arg Arg Arg Pro Phe Arg  
 930 935 940  
 Gln Ile Gln Val Leu Glu Pro Leu Asn Leu Leu Ile Thr Ile Ser Gly  
 945 950 955 960  
 His Lys Asn Arg Leu Arg Val Tyr His Leu Thr Trp Leu Arg Asn Lys  
 965 970 975  
 Ile Leu Asn Asn Asp Pro Glu Ser Lys Arg Arg Gln Glu Glu Met Leu  
 980 985 990

120

Lys Thr Glu Glu Ala Cys Lys Ala Ile Asp Lys Leu Thr Gly Cys Glu  
 995 1000 1005  
 His Phe Ser Val Leu Gln His Glu Glu Thr Thr Tyr Ile Ala Ile Ala  
 1010 1015 1020  
 Leu Lys Ser Ser Ile His Leu Tyr Ala Trp Ala Pro Lys Ser Phe Asp  
 1025 1030 1035 1040  
 Glu Ser Thr Ala Ile Lys Val Phe Pro Thr Leu Asp His Lys Pro Val  
 1045 1050 1055  
 Thr Val Asp Leu Ala Ile Gly Ser Glu Lys Arg Leu Lys Ile Phe Phe  
 1060 1065 1070  
 Ser Ser Ala Asp Gly Tyr His Leu Ile Asp Ala Glu Ser Glu Val Met  
 1075 1080 1085  
 Ser Asp Val Thr Leu Pro Lys Asn Pro Leu Glu Ile Ile Ile Pro Gln  
 1090 1095 1100  
 Asn Ile Ile Ile Leu Pro Asp Cys Leu Gly Ile Gly Met Met Leu Thr  
 1105 1110 1115 1120  
 Phe Asn Ala Glu Ala Leu Ser Val Glu Ala Asn Glu Gln Leu Phe Lys  
 1125 1130 1135  
 Lys Ile Leu Glu Met Trp Lys Asp Ile Pro Ser Ser Ile Ala Phe Glu  
 1140 1145 1150  
 Cys Thr Gln Arg Thr Thr Gly Trp Gly Gln Lys Ala Ile Glu Val Arg  
 1155 1160 1165  
 Ser Leu Gln Ser Arg Val Leu Glu Ser Glu Leu Lys Arg Arg Ser Ile  
 1170 1175 1180  
 Lys Lys Leu Arg Phe Leu Cys Thr Arg Gly Asp Lys Leu Phe Phe Thr  
 1185 1190 1195 1200  
 Ser Thr Leu Arg Asn His His Ser Arg Val Tyr Phe Met Thr Leu Gly  
 1205 1210 1215  
 Lys Leu Glu Glu Leu Gln Ser Asn Tyr Asp Val  
 1220 1225

<210> 106  
 <211> 2962  
 <212> DNA  
 <213> Full Length Mammalian (Human) GEK2  
 <400> 106

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cgaatatgag	cacgtccgcc	gcgacctgga	ccccaacgag	gtgtgggaga	tcgtggcgga	180
gctggggcag	ggcgcccttcg	gcaaggttta	caaggccaag	aataaggaga	cgggtgcttt	240
ggctgcgggc	aaagtcatcg	aaaccaagag	tgaggaggag	ctggaggact	acatcgtgga	300
gattgagatc	ctggccacct	gcgaccaccc	ctacattgtg	aagctcctgg	gagcctaacta	360
tcacgacggg	aagctgtgga	tcatgattga	gttctgtcca	gggggagccg	tggacgccat	420
catgtctggag	ctggacagag	gcctcacgga	gccccagata	caggtggttt	gccgccagat	480
gctagaagcc	ctcaacttcc	tgcacagcaa	gaggatcatc	caccgagatc	tgaaagctgg	540
caacgtgctg	atgacctctg	agggagacat	caggctggct	gactttgggt	tgtctgccaa	600
gaatctgaag	actctacaga	aacgagattc	cttcacggc	acgccttact	ggatggcccc	660
cgaagtggtc	atgtgtgaga	ccatgaaaga	cacgccctac	gactacaaag	ccgacatctg	720
gtccctgggc	atcacgctga	ttgagatggc	ccagatcgag	ccgccacacc	acgagctcaa	780
ccccatgcgg	gtcctgctaa	agatcgccaa	gtcggaccct	cccacgctgc	tcacgccctc	840
caagtggctc	gtagagtcc	gtgacttcct	gaagatagcc	ctggataaga	accagaaac	900
ccgacccagt	gccgcgcagc	tgtctggagca	tccttcgtc	agcagcatca	ccagtaacaa	960
ggctctgcgg	gagctggtgg	ctgaggccaa	ggccgaggtg	atggaagaga	tcgaagacgg	1020
ccgggatgag	ggggaagagg	aggacgccgt	ggatgccgcc	tccacctgg	agaaccatac	1080
tcagaactcc	tctgaggtga	gtccgccaa	cctcaatgct	gacaagcctc	tcgaggagtc	1140
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caagagggac	tcggactgca	gcagcctctg	cacctctgag	agcatggact	atggtaccaa	1560
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gcagcaagtg	gagaagatgg	agcaagacca	tgccgtgcgc	cgccgggagg	aggccaggcg	1980
gatccgcctg	gagcaggatc	gggactacac	cagggtccaa	gagcagctca	aactgatgaa	2040
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gcagaagatg	gaggagcaca	cgcagaaaaa	gcagcttctt	gaccgggact	ttgtagccaa	2160
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ggaaaaggcg	cggtgcccc	agatccagag	gagtgagggc	aagacgcgca	tggccatgta	2520
caagaagagc	ctccacatca	acggcggggg	cagcgcagct	gagcagcgtg	agaagatcaa	2580
gcagtctctc	cagcaggagg	agaagaggca	gaagtcggag	cggctgcagc	aacagcagaa	2640
acacgagaac	cagatgcggg	acatgctggc	gcagtgcgag	agcaacatga	gcgagctgca	2700
gcagctgcag	aatgaaaaagt	gccacctcct	ggtagagcac	gaaaccaga	aactgaagc	2760
cctggatgag	agccataacc	agaacctgaa	ggaatggcgg	gacaagcttc	ggccgcgcaa	2820
gaaggctctg	gaagaggatc	tgaaccagaa	gaagcgggag	caggagatgt	tcttcaagct	2880
gagcgaggag	gcggagtgcc	caaacccctc	caccccaagc	aaggccgcca	agttcttccc	2940
ctacagctct	ggggatgctt	cc				2962

122

<210> 107  
 <211> 968  
 <212> PRT  
 <213> Full Length Mammalian (Human) GEK2  
 <400> 107

Met	Ala	Phe	Ala	Asn	Phe	Arg	Arg	Ile	Leu	Arg	Leu	Ser	Thr	Phe	Glu	1	5	10	15
Lys	Arg	Lys	Ser	Arg	Glu	Tyr	Glu	His	Val	Arg	Arg	Asp	Leu	Asp	Pro	20	25	30	
Asn	Glu	Val	Trp	Glu	Ile	Val	Gly	Glu	Leu	Gly	Asp	Gly	Ala	Phe	Gly	35	40	45	
Lys	Val	Tyr	Lys	Ala	Lys	Asn	Lys	Glu	Thr	Gly	Ala	Leu	Ala	Ala	Ala	50	55	60	
Lys	Val	Ile	Glu	Thr	Lys	Ser	Glu	Glu	Glu	Leu	Glu	Asp	Tyr	Ile	Val	65	70	75	80
Glu	Ile	Glu	Ile	Leu	Ala	Thr	Cys	Asp	His	Pro	Tyr	Ile	Val	Lys	Leu	85	90	95	
Leu	Gly	Ala	Tyr	Tyr	His	Asp	Gly	Lys	Leu	Trp	Ile	Met	Ile	Glu	Phe	100	105	110	
Cys	Pro	Gly	Gly	Ala	Val	Asp	Ala	Ile	Met	Leu	Glu	Leu	Asp	Arg	Gly	115	120	125	
Leu	Thr	Glu	Pro	Gln	Ile	Gln	Val	Val	Cys	Arg	Gln	Met	Leu	Glu	Ala	130	135	140	
Leu	Asn	Phe	Leu	His	Ser	Lys	Arg	Ile	Ile	His	Arg	Asp	Leu	Lys	Ala	145	150	155	160
Gly	Asn	Val	Leu	Met	Thr	Leu	Glu	Gly	Asp	Ile	Arg	Leu	Ala	Asp	Phe	165	170	175	
Gly	Val	Ser	Ala	Lys	Asn	Leu	Lys	Thr	Leu	Gln	Lys	Arg	Asp	Ser	Phe	180	185	190	
Ile	Gly	Thr	Pro	Tyr	Trp	Met	Ala	Pro	Glu	Val	Val	Met	Cys	Glu	Thr	195	200	205	
Met	Lys	Asp	Thr	Pro	Tyr	Asp	Tyr	Lys	Ala	Asp	Ile	Trp	Ser	Leu	Gly	210	215	220	
Ile	Thr	Leu	Ile	Glu	Met	Ala	Gln	Ile	Glu	Pro	Pro	His	His	Glu	Leu	225	230	235	240
Asn	Pro	Met	Arg	Val	Leu	Leu	Lys	Ile	Ala	Lys	Ser	Asp	Pro	Pro	Thr	245	250	255	

123

Leu Leu Thr Pro Ser Lys Trp Ser Val Glu Phe Arg Asp Phe Leu Lys  
 260 265 270  
 Ile Ala Leu Asp Lys Asn Pro Glu Thr Arg Pro Ser Ala Ala Gln Leu  
 275 280 285  
 Leu Glu His Pro Phe Val Ser Ser Ile Thr Ser Asn Lys Ala Leu Arg  
 290 295 300  
 Glu Leu Val Ala Glu Ala Lys Ala Glu Val Met Glu Glu Ile Glu Asp  
 305 310 315 320  
 Gly Arg Asp Glu Gly Glu Glu Glu Asp Ala Val Asp Ala Ala Ser Thr  
 325 330 335  
 Leu Glu Asn His Thr Gln Asn Ser Ser Glu Val Ser Pro Pro Ser Leu  
 340 345 350  
 Asn Ala Asp Lys Pro Leu Glu Glu Ser Pro Ser Thr Pro Leu Ala Pro  
 355 360 365  
 Ser Gln Ser Gln Asp Ser Val Asn Glu Pro Cys Ser Gln Pro Ser Gly  
 370 375 380  
 Asp Arg Ser Leu Gln Thr Thr Ser Pro Pro Val Val Ala Pro Gly Asn  
 385 390 395 400  
 Glu Asn Gly Leu Ala Val Pro Val Pro Leu Arg Lys Ser Arg Pro Val  
 405 410 415  
 Ser Met Asp Ala Arg Ile Gln Val Ala Gln Glu Lys Gln Val Ala Glu  
 420 425 430  
 Gln Gly Gly Asp Leu Ser Pro Ala Ala Asn Arg Ser Gln Lys Ala Ser  
 435 440 445  
 Gln Ser Arg Pro Asn Ser Ser Ala Leu Glu Thr Leu Gly Gly Glu Lys  
 450 455 460  
 Leu Ala Asn Gly Ser Leu Glu Pro Pro Ala Gln Ala Ala Pro Gly Pro  
 465 470 475 480  
 Ser Lys Arg Asp Ser Asp Cys Ser Ser Leu Cys Thr Ser Glu Ser Met  
 485 490 495  
 Asp Tyr Gly Thr Asn Leu Ser Thr Asp Leu Ser Leu Asn Lys Glu Met  
 500 505 510  
 Gly Ser Leu Ser Ile Lys Asp Pro Lys Leu Tyr Lys Lys Thr Leu Lys  
 515 520 525  
 Arg Thr Arg Lys Phe Val Val Asp Gly Val Glu Val Ser Ile Thr Thr  
 530 535 540  
 Ser Lys Ile Ile Ser Glu Asp Glu Lys Lys Asp Glu Glu Met Arg Phe  
 545 550 555 560

Leu Arg Arg Gln Glu Leu Arg Glu Leu Arg Leu Leu Gln Lys Glu Glu  
 565 570 575  
 His Arg Asn Gln Thr Gln Leu Ser Asn Lys His Glu Leu Gln Leu Glu  
 580 585 590  
 Gln Met His Lys Arg Phe Glu Gln Glu Ile Asn Ala Lys Lys Lys Phe  
 595 600 605  
 Phe Asp Thr Glu Leu Glu Asn Leu Glu Arg Gln Gln Lys Gln Gln Val  
 610 615 620  
 Glu Lys Met Glu Gln Asp His Ala Val Arg Arg Arg Glu Glu Ala Arg  
 625 630 635 640  
 Arg Ile Arg Leu Glu Gln Asp Arg Asp Tyr Thr Arg Phe Gln Glu Gln  
 645 650 655  
 Leu Lys Leu Met Lys Lys Glu Val Lys Asn Glu Val Glu Lys Leu Pro  
 660 665 670  
 Arg Gln Gln Arg Lys Glu Ser Met Lys Gln Lys Met Glu Glu His Thr  
 675 680 685  
 Gln Lys Lys Gln Leu Leu Asp Arg Asp Phe Val Ala Lys Gln Lys Glu  
 690 695 700  
 Asp Leu Glu Leu Ala Met Lys Arg Leu Thr Thr Asp Asn Arg Arg Glu  
 705 710 715 720  
 Ile Cys Asp Lys Glu Arg Glu Cys Leu Met Lys Lys Gln Glu Leu Leu  
 725 730 735  
 Arg Asp Arg Glu Ala Ala Leu Trp Glu Met Glu Glu His Gln Leu Gln  
 740 745 750  
 Glu Arg His Gln Leu Val Lys Gln Gln Leu Lys Asp Gln Tyr Phe Leu  
 755 760 765  
 Gln Arg His Glu Leu Leu Arg Lys His Glu Lys Glu Arg Glu Gln Met  
 770 775 780  
 Gln Arg Tyr Asn Gln Arg Met Ile Glu Gln Leu Lys Val Arg Gln Gln  
 785 790 795 800  
 Gln Glu Lys Ala Arg Leu Pro Lys Ile Gln Arg Ser Glu Gly Lys Thr  
 805 810 815  
 Arg Met Ala Met Tyr Lys Lys Ser Leu His Ile Asn Gly Gly Gly Ser  
 820 825 830  
 Ala Ala Glu Gln Arg Glu Lys Ile Lys Gln Phe Ser Gln Gln Glu Glu  
 835 840 845



125

Lys Arg Gln Lys Ser Glu Arg Leu Gln Gln Gln Gln Lys His Glu Asn  
 850 855 860  
 Gln Met Arg Asp Met Leu Ala Gln Cys Glu Ser Asn Met Ser Glu Leu  
 865 870 875 880  
 Gln Gln Leu Gln Asn Glu Lys Cys His Leu Leu Val Glu His Glu Thr  
 885 890 895  
 Gln Lys Leu Lys Ala Leu Asp Glu Ser His Asn Gln Asn Leu Lys Glu  
 900 905 910  
 Trp Arg Asp Lys Leu Arg Pro Arg Lys Lys Ala Leu Glu Glu Asp Leu  
 915 920 925  
 Asn Gln Lys Lys Arg Glu Gln Glu Met Phe Phe Lys Leu Ser Glu Glu  
 930 935 940  
 Ala Glu Cys Pro Asn Pro Ser Thr Pro Ser Lys Ala Ala Lys Phe Phe  
 945 950 955 960  
 Pro Tyr Ser Ser Gly Asp Ala Ser  
 965

<210> 108  
 <211> 11  
 <212> PRT  
 <213> Mammalian (human) ZC1 and/or ZC3  
 <220>  
 <223> "Xaa can stand for any amino acid"

<400> 108

Leu Xaa Leu Xaa Leu Xaa Leu Xaa Leu Xaa Leu  
 1 5 10

<210> 109  
 <211> 20  
 <212> DNA  
 <213> Artificial Sequence  
 <220>  
 <223> Synthesized nucleic acid molecule

<400> 109

gcagcaagtg gagaagatgg

20

<210> 110

126

<211> 22  
<212> DNA  
<213> Artificial Sequence  
  
<220>  
<223> Synthesized nucleic acid molecule  
  
<400> 110

ggaagcatcc ccagagctgt ag

22

<210> 111  
<211> 12  
<212> PRT  
<213> Mammalian (Human) STLK2  
  
<400> 111

Glu Lys Phe Gln Lys Cys Ser Ala Asp Glu Ser Pro  
1 5 10

<210> 112  
<211> 16  
<212> PRT  
<213> Mammalian (Human) STLK4  
  
<400> 112

Ser Ile Ser Asn Ser Glu Leu Phe Pro Thr Thr Asp Pro Val Gly Thr  
1 5 10 15

<210> 113  
<211> 9  
<212> PRT  
<213> Mammalian (Human) SULU1  
  
<400> 113

Leu Asp Phe Pro Lys Glu Asp Tyr Arg  
1 5

<210> 114  
<211> 12  
<212> PRT  
<213> Mammalian (Human) SULU1  
  
<400> 114

127

His Gly Asp Pro Arg Pro Glu Pro Arg Pro Thr Gln  
1 5 10

<210> 115  
<211> 14  
<212> PRT  
<213> Mammalian (Human) SULU3

<400> 115

Pro Ser Thr Asn Arg Ala Gly Ser Leu Lys Asp Pro Glu Cys  
1 5 10

<210> 116  
<211> 19  
<212> PRT  
<213> Mammalian (Human) SULU3

<400> 116

Asp Pro Arg Thr Arg Ala Ser Asp Pro Gln Ser Pro Pro Gln Val Ser  
1 5 10 15

Arg His Lys

<210> 117  
<211> 16  
<212> PRT  
<213> Mammalian (Human) PAK4

<400> 117

Cys Leu Val Pro Leu Ile Gln Leu Tyr Arg Lys Gln Thr Ser Thr Cys  
1 5 10 15

<210> 118  
<211> 9  
<212> PRT  
<213> Mammalian (Human) PAK5

<400> 118

Pro Leu Met Arg Gln Asn Arg Thr Arg  
1 5

128

<210> 119  
 <211> 16  
 <212> PRT  
 <213> Mammalian (Human) PAK5

<400> 119

Ser Gly Asp Arg Arg Arg Ala Gly Pro Glu Lys Arg Pro Lys Ser Ser  
 1 5 10 15

<210> 120  
 <211> 16  
 <212> PRT  
 <213> Mammalian (Human) PAK5

<400> 120

Cys Arg Arg Lys Ser Leu Val Gly Thr Pro Tyr Trp Met Ala Pro Glu  
 1 5 10 15

<210> 121  
 <211> 20  
 <212> PRT  
 <213> Mammalian (Human) ZC1

<400> 121

Arg Thr Val Gly Arg Arg Asn Thr Phe Ile Gly Thr Pro Pro Tyr Trp  
 1 5 10 15

Met Ala Pro Glu  
 20

<210> 122  
 <211> 15  
 <212> PRT  
 <213> Mammalian (Human) KHS1

<400> 122

Lys Arg Lys Ser Phe Ile Gly Thr Pro Tyr Trp Met Ala Pro Glu  
 1 5 10 15

129

<210> 123  
<211> 15  
<212> PRT  
<213> Mammalian (Human) STLK2

&lt;400&gt; 123

Lys Arg Asn Thr Phe Val Gly Thr Pro Phe Trp Met Ala Pro Glu  
1 5 10 15

<210> 124  
<211> 15  
<212> PRT  
<213> Mammalian (Human) SULU1

&lt;400&gt; 124

Pro Ala Asn Ser Phe Val Gly Thr Pro Tyr Trp Met Ala Pro Glu  
1 5 10 15

<210> 125  
<211> 15  
<212> PRT  
<213> Mammalian (Human) ZC1

&lt;400&gt; 125

Arg Arg Asn Thr Phe Ile Gly Thr Pro Tyr Trp Met Ala Pro Glu  
1 5 10 15

<210> 126  
<211> 15  
<212> PRT  
<213> Mammalian (Human) ZC1

&lt;400&gt; 126

Arg Arg Asn Thr Phe Ile Gly Thr Pro Tyr Trp Met Ala Pro Glu  
1 5 10 15

<210> 127  
<211> 18  
<212> PRT  
<213> Mammalian (Human) STLK4

130

&lt;400&gt; 127

Arg	Asn	Lys	Val	Arg	Lys	Thr	Phe	Val	Gly	Thr	Pro	Cys	Trp	Met	Ala
1				5					10					15	

Pro Glu

&lt;210&gt; 128

&lt;211&gt; 22

&lt;212&gt; DNA

&lt;213&gt; Mammalian (Human) STLK3

&lt;400&gt; 128

ctcccatcttc ctagcaaaat ca

22

&lt;210&gt; 129

&lt;211&gt; 22

&lt;212&gt; DNA

&lt;213&gt; Mammalian (Human) STLK3

&lt;400&gt; 129

agaggcagta ttgtcagatg ta

22

&lt;210&gt; 130

&lt;211&gt; 22

&lt;212&gt; DNA

&lt;213&gt; Mammalian (Human) STLK4

&lt;400&gt; 130

ccacacatgc gtatctctgt tg

22

&lt;210&gt; 131

&lt;211&gt; 24

&lt;212&gt; DNA

&lt;213&gt; Mammalian (Human) STLK4

&lt;400&gt;

131

ttgctagaat tcacatcagg taca

24

<210> 132  
<211> 22  
<212> DNA  
<213> Mammalian (Human) ZC1

&lt;400&gt; 132

atccctggat cacactgctt ct

22

<210> 133  
<211> 22  
<212> DNA  
<213> Mammalian (Human) ZC1

&lt;400&gt; 133

caaggtgttc ttgcctctg tt

22

<210> 134  
<211> 21  
<212> DNA  
<213> Mammalian (Human) ZC2

&lt;400&gt; 134

agatggactg tactgggagg g

21

<210> 135  
<211> 22  
<212> DNA  
<213> Mammalian (Human) ZC2

&lt;400&gt; 135

agaagagcac ttggcactta tc

22

<210> 136  
<211> 20  
<212> DNA  
<213> Mammalian (Human) ZC3

132

&lt;400&gt; 136

catcatgaac tggtagcggg

20

&lt;210&gt; 137

&lt;211&gt; 23

&lt;212&gt; DNA

&lt;213&gt; Mammalian (Human) ZC3

&lt;400&gt; 137

ccagtgaat caaaccagta aaa

23

&lt;210&gt; 138

&lt;211&gt; 24

&lt;212&gt; DNA

&lt;213&gt; Mammalian (Human) SULU1

&lt;400&gt; 138

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24

&lt;210&gt; 139

&lt;211&gt; 23

&lt;212&gt; DNA

&lt;213&gt; Mammalian (Human) SULU1

&lt;400&gt; 139

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23

&lt;210&gt; 140

&lt;211&gt; 24

&lt;212&gt; DNA

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&lt;400&gt; 140

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24

&lt;210&gt; 141



133

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23

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23

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20

134

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20

<210> 147  
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<213> T7 phage

<400> 147

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21

CLAIMS

1. An isolated, enriched or purified nucleic acid molecule encoding a STLK2 kinase polypeptide said nucleic acid molecule comprising a nucleotide sequence that:
  - (a) encodes the complete amino acid sequence as set forth in SEQ ID NO:5;
  - (b) is the complement of all of the nucleotide sequence of (a);
  - (c) encodes at least 40 contiguous amino acids of the amino acid sequence set forth in SEQ ID NO:5 and having kinase activity;
  - (d) is the complement of all of the nucleotide sequence of (c);
  - (e) encodes a polypeptide having kinase activity comprising the amino acid sequence set forth in SEQ ID NO:5 except that it lacks one or more of the domains defined by amino acid segments 1-21, or 275-416 of SEQ ID NO:5;
  - (f) is the complement of all of the nucleotide sequence of (e).
2. The nucleic acid molecule of claim 1 wherein said nucleic acid molecule is isolated, enriched or purified from a mammal.
3. The nucleic acid molecule of claim 2 wherein said mammal is a human.
4. The nucleic acid molecule of any of claims 1 to 3, further comprising a vector or promoter effective to initiate transcription in a host cell.

5. A nucleic acid probe for the detection of nucleic acid encoding a STLK2 kinase polypeptide in a sample, said probe specifically hybridizing to a nucleic acid molecule that encodes the complete amino acid sequence as set forth in SEQ ID NO:5 or encodes at least 40 contiguous amino acids of the amino acid sequence set forth in SEQ ID NO:5 and having kinase activity.

6. A recombinant cell comprising a nucleic acid molecule encoding a STLK2 kinase polypeptide having the complete amino acid sequence as set forth in SEQ ID NO:5 or encodes at least 40 contiguous amino acids of the amino acid sequence set forth in SEQ ID NO:5 and having kinase activity.

7. An isolated, enriched or purified STLK2 kinase polypeptide having the amino acid sequence set forth in SEQ ID NO:5 or a fragment thereof comprising at least 40 contiguous amino acids of SEQ ID NO:5 and having kinase activity.

8. An isolated, enriched or purified STLK2 kinase polypeptide having the amino acid sequence set forth in SEQ ID NO:5 except that it lacks one or more of the domains defined by amino acid segments 1-21, or 275-416 of SEQ ID NO:5 and having a kinase activity.

9. The kinase polypeptide molecule of claim 7 or claim 8 wherein said polypeptide is isolated, enriched or purified from a mammal.

10. The kinase polypeptide molecule of claim 9 wherein said mammal is a human.

11. An antibody or antibody fragment having specific binding affinity to a STLK2 kinase polypeptide having the complete amino acid sequence set forth in SEQ ID NO:5, a fragment thereof comprising at least 40 contiguous amino acids of SEQ ID NO:5 and having kinase activity or having the amino acid sequence set forth in SEQ ID NO:5 except that it lacks one or more of the domains defined by amino acid segments 1-21, or 275-416 of SEQ ID NO:5.

12. A hybridoma which produces an antibody having specific binding affinity to a STLK2 kinase polypeptide having the complete amino acid sequence set forth in SEQ ID NO:5, a fragment thereof comprising at least 40 contiguous amino acids of SEQ ID NO:5 and having kinase activity or having the amino acid sequence set forth in SEQ ID NO:5 except that it lacks one or more of the domains defined by amino acid segments 1-21, or 275-416 of SEQ ID NO:5.

13. A method for identifying a substance that modulates kinase activity comprising the steps of:

- (a) contacting a STLK2 kinase polypeptide having the complete amino acid sequence set forth in SEQ ID NO:5, a fragment thereof comprising at least 40 contiguous amino acids of SEQ ID NO:5 and having kinase activity or having the amino acid sequence set forth in SEQ ID NO:5 except that it lacks one or more of the domains defined by amino acid segments 1-21, or 275-416 of SEQ ID NO:5 with a test substance;
- (b) measuring the activity of said polypeptide; and
- (c) determining whether said substance modulates the activity of said polypeptide.

14. A method for identifying a substance that modulates kinase activity comprising the steps of:

- (a) expressing a STLK2 kinase polypeptide having the complete amino acid sequence set forth in SEQ ID NO:5, a fragment thereof comprising at least 40 contiguous amino acids of SEQ ID NO:5 and having kinase activity or having the amino acid sequence set forth in SEQ ID NO:5 except that it lacks one or more of the domains defined by amino acid segments 1-21, or 275-416 of SEQ ID NO:5;
- (b) adding a test substance to said cell; and
- (c) monitoring a change in cell phenotype or the interaction between said polypeptide and a natural binding partner.

15. A method for detection of a STLK2 kinase polypeptide in a sample as a diagnostic tool for a disease or disorder wherein said method comprises:

- (a) contacting said sample with a nucleic acid probe which specifically hybridizes, under hybridization conditions which are at least as stringent as hybridization in 50% formamide, 5X SSC, 50mM NaH<sub>2</sub>PO<sub>4</sub>, pH6.8, 0.5% SDS, 0.1 mg/ml sonicated salmon sperm DNA and 5X Denhart solution at 42°C; overnight washing with 2X SSC, 0.1% SDS at 45°C; and washing with 0.2X SSC, 0.1% SDS at 45°C to a STLK2 kinase nucleic acid target region that,

encodes the complete amino acid sequence as set forth in SEQ ID NO:5 or is the complement of all of the nucleotides thereof, encodes at least 40 contiguous amino acids of the amino acid sequence set forth in SEQ ID NO:5 and having kinase activity or the complement of all of the nucleotides thereof, or encodes a polypeptide having kinase activity comprising the amino acid sequence set

forth in SEQ ID NO:5 except that it lacks one or more of the domains defined by amino acid segments 1-21, or 275-416 of SEQ ID NO:5 or is the complement of all of the nucleotides thereof; and

(b) detecting the presence of the probe:target region hybrid as an indication of said disease.

16. The method of claim 15 wherein said disease or disorder is selected from the group consisting of immune-related diseases and disorders, organ transplantation, myocardial infarction, cardiovascular disease, stroke, renal failure, oxidative stress-related neurodegenerative disorders and cancer.

17. A method for detection of a STLK2 kinase polypeptide in a sample as a diagnostic tool for a disease or disorder wherein said method comprises:

(a) comparing a nucleic acid target region encoding said STLK2 kinase polypeptide in a sample, said kinase polypeptide having an amino acid sequence as set forth in SEQ ID NO:5, at least 40 contiguous amino acids thereof and having kinase activity, or the amino acid sequence as set forth in SEQ ID NO:5 except that it lacks one or more of the domains defined by amino acid segments 1-21, or 275-416 of SEQ ID NO:5, with a control nucleic acid target region encoding said STLK2 kinase polypeptide; and

(b) detecting differences in sequence or amount between said target region and said control target region as an indication of said disease or disorder.

18. The method of claim 17 wherein said disease or disorder is selected from the group consisting of immune-related diseases and disorders, organ transplantation, myocardial infarction, cardiovascular disease, stroke,

renal failure, oxidative stress-related neurodegenerative disorders and cancer.

19. A method for treating a disease or disorder by administering to a patient in need of such treatment a substance that modulates the activity of a STLK2 kinase having an amino acid sequence as set forth in SEQ ID NO:5, at least 40 contiguous amino acids thereof and having kinase activity, or the amino acid sequence as set forth in SEQ ID NO:5 except that it lacks one or more of the domains defined by amino acid segments 1-21, or 275-416 of SEQ ID NO:5.

20. The method of claim 19 wherein said disease or disorder is selected from the group consisting of immune-related diseases and disorders, organ transplantation, myocardial infarction, cardiovascular disease, stroke, renal failure, oxidative stress-related neurodegenerative disorders and cancer.

21. The method of claim 19 or claim 20 wherein said substance modulates kinase activity *in vitro*.

22. The method of claim 21, wherein said substance is a kinase inhibitor.

23. An isolated, enriched or purified nucleic acid molecule encoding a STLK4 kinase polypeptide said nucleic acid molecule comprising a nucleotide sequence that:

(a) encodes the complete amino acid sequence as set forth in SEQ ID NO:7;

(b) is the complement of all of the nucleotide sequence of (a);



(c) encodes at least 40 contiguous amino acids of the amino acid sequence set forth in SEQ ID NO:7 and having kinase activity;

(d) is the complement of all of the nucleotide sequence of (c);

(e) encodes a polypeptide having kinase activity comprising the amino acid sequence set forth in SEQ ID NO:7 except that it lacks one or more of the domains defined by amino acid segments 179-414 of SEQ ID NO:7;

(f) is the complement of all of the nucleotide sequence of (e).

24. The nucleic acid molecule of claim 23 wherein said nucleic acid molecule is isolated, enriched or purified from a mammal.

25. The nucleic acid molecule of claim 24 wherein said mammal is a human.

26. The nucleic acid molecule of any of claims 23 to 25, further comprising a vector or promoter effective to initiate transcription in a host cell.

27. A nucleic acid probe for the detection of nucleic acid encoding a STLK4 kinase polypeptide in a sample, said probe specifically hybridizing to a nucleic acid molecule that encodes the complete amino acid sequence as set forth in SEQ ID NO:7 or encodes at least 40 contiguous amino acids of the amino acid sequence set forth in SEQ ID NO:7 and having kinase activity.

28. A recombinant cell comprising a nucleic acid molecule encoding a STLK4 kinase polypeptide having the complete amino acid sequence as set forth in SEQ ID NO:7

or encodes at least 40 contiguous amino acids of the amino acid sequence set forth in SEQ ID NO:7 and having kinase activity.

29. An isolated, enriched or purified STLK4 kinase polypeptide having the amino acid sequence set forth in SEQ ID NO:7 or a fragment thereof comprising at least 40 contiguous amino acids of SEQ ID NO:7 and having kinase activity.

30. An isolated, enriched or purified STLK4 kinase polypeptide having the amino acid sequence set forth in SEQ ID NO:7 except that it lacks one or more of the domains defined by amino acid segments 179-414 of SEQ ID NO:7 and having kinase activity.

31. The kinase polypeptide molecule of claim 29 or claim 30 wherein said polypeptide is isolated, enriched or purified from a mammal.

32. The kinase polypeptide molecule of claim 31 wherein said mammal is a human.

33. An antibody or antibody fragment having specific binding affinity to a STLK4 kinase polypeptide having the complete amino acid sequence set forth in SEQ ID NO:7, a fragment thereof comprising at least 40 contiguous amino acids of SEQ ID NO:7 and having kinase activity or having the amino acid sequence set forth in SEQ ID NO:7 except that it lacks one or more of the domains defined by amino acid segments 179-414 of SEQ ID NO:7.

34. A hybridoma which produces an antibody having

specific binding affinity to a STLK4 kinase polypeptide having the complete amino acid sequence set forth in SEQ ID NO:7, a fragment thereof comprising at least 40 contiguous amino acids of SEQ ID NO:7 and having kinase activity or having the amino acid sequence set forth in SEQ ID NO:7 except that it lacks one or more of the domains defined by amino acid segments 179-414 of SEQ ID NO:7.

35. A method for identifying a substance that modulates kinase activity comprising the steps of:

- (a) contacting a STLK4 kinase polypeptide having the complete amino acid sequence set forth in SEQ ID NO:4, a fragment thereof comprising at least 40 contiguous amino acids of SEQ ID NO:7 and having kinase activity or having the amino acid sequence set forth in SEQ ID NO:7 except that it lacks one or more of the domains defined by amino acid segments 179-414 of SEQ ID NO:7 with a test substance;
- (b) measuring the activity of said polypeptide; and
- (c) determining whether said substance modulates the activity of said polypeptide.

36. A method for identifying a substance that modulates kinase activity comprising the steps of:

- (a) expressing a STLK4 kinase polypeptide having the complete amino acid sequence set forth in SEQ ID NO:7, a fragment thereof comprising at least 40 contiguous amino acids of SEQ ID NO:7 and having kinase activity or having the amino acid sequence set forth in SEQ ID NO:7 except that it lacks one or more of the domains defined by amino acid segments 179-414 of SEQ ID NO:7;
- (b) adding a test substance to said cell; and

(c) monitoring a change in cell phenotype or the interaction between said polypeptide and a natural binding partner.

37. A method for detection of a STLK4 kinase polypeptide in a sample as a diagnostic tool for a disease or disorder wherein said method comprises:

(a) contacting said sample with a nucleic acid probe which specifically hybridizes, under hybridization conditions which are at least as stringent as hybridization in 50% formamide, 5X SSC, 50mM NaH<sub>2</sub>PO<sub>4</sub>, pH6.8, 0.5% SDS, 0.1 mg/ml sonicated salmon sperm DNA and 5X Denhart solution at 42°C; overnight washing with 2X SSC, 0.1%SDS at 45°C; and washing with 0.2X SSC, 0.1% SDS at 45°C to a STLK2 kinase nucleic acid target region that,

encodes the complete amino acid sequence as set forth in SEQ ID NO:7 or is the complement of all of the nucleotides thereof, encodes at least 40 contiguous amino acids of the amino acid sequence set forth in SEQ ID NO:7 and having kinase activity or the complement of all of the nucleotides thereof, or encodes a polypeptide having kinase activity comprising the amino acid sequence set forth in SEQ ID NO:5 except that it lacks one or more of the domains defined by amino acid segments 179-414 of SEQ ID NO:7 or is the complement of all of the nucleotides thereof; and

(b) detecting the presence of the probe:target region hybrid as an indication of said disease.

38. The method of claim 37 wherein said disease or disorder is selected from the group consisting of immune-related diseases and disorders, organ transplantation, myocardial infarction, cardiovascular disease, stroke,

renal failure, oxidative stress-related neurodegenerative disorders and cancer.

39. A method for detection of a STLK4 kinase polypeptide in a sample as a diagnostic tool for a disease or disorder wherein said method comprises:

(a) comparing a nucleic acid target region encoding said STLK4 kinase polypeptide in a sample, said kinase polypeptide having an amino acid sequence as set forth in SEQ ID NO:7, at least 40 contiguous amino acids thereof and having kinase activity, or the amino acid sequence as set forth in SEQ ID NO:7 except that it lacks one or more of the domains defined by amino acid segments 179-414 of SEQ ID NO:7, with a control nucleic acid target region encoding said STLK4 kinase polypeptide; and

(b) detecting differences in sequence or amount between said target region and said control target region as an indication of said disease or disorder.

40. The method of claim 39 wherein said disease or disorder is selected from the group consisting of immune-related diseases and disorders, organ transplantation, myocardial infarction, cardiovascular disease, stroke, renal failure, oxidative stress-related neurodegenerative disorders and cancer.

41. A method for treating a disease or disorder by administering to a patient in need of such treatment a substance that modulates the activity of a STLK4 kinase having an amino acid sequence as set forth in SEQ ID NO:7, at least 40 contiguous amino acids thereof and having kinase activity, or the amino acid sequence as set forth in SEQ ID NO:7 except that it lacks one or more of the domains defined by amino acid segments 179-414 of SEQ

ID NO:7.

42. The method of claim 41 wherein said disease or disorder is selected from the group consisting of immune-related diseases and disorders, organ transplantation, myocardial infarction, cardiovascular disease, stroke, renal failure, oxidative stress-related neurodegenerative disorders and cancer.

43. The method of claim 41 or claim 42 wherein said substance modulates kinase activity *in vitro*.

44. The method of claim 43, wherein said substance is a kinase inhibitor.

45. An isolated, enriched or purified nucleic acid molecule encoding a ZC1 kinase polypeptide said nucleic acid molecule comprising a nucleotide sequence that:

(a) encodes the complete amino acid sequence as set forth in SEQ ID NO:13;

(b) is the complement of all of the nucleotide sequence of (a);

(c) encodes at least 250 contiguous amino acids of the amino acid sequence set forth in SEQ ID NO:13 and having kinase activity;

(d) is the complement of all of the nucleotide sequence of (c);

(e) encodes a polypeptide having kinase activity comprising the amino acid sequence set forth in SEQ ID NO:13 except that it lacks one or more of the domains defined by amino acid segments 1-22, 290-526, 527-640, 641-896, or 897-1239 of SEQ ID NO:13;

(f) is the complement of all of the nucleotide sequence of (e).

46. The nucleic acid molecule of claim 45 wherein said nucleic acid molecule is isolated, enriched or purified from a mammal.

47. The nucleic acid molecule of claim 46 wherein said mammal is a human.

48. The nucleic acid molecule of any of claims 45 to 47, further comprising a vector or promoter effective to initiate transcription in a host cell.

49. A nucleic acid probe for the detection of nucleic acid encoding a ZC1 kinase polypeptide in a sample, said probe specifically hybridizing to a nucleic acid molecule that encodes the complete amino acid sequence as set forth in SEQ ID NO: 13 or encodes at least 250 contiguous amino acids of the amino acid sequence set forth in SEQ ID NO:13 and having kinase activity.

50. A recombinant cell comprising a nucleic acid molecule encoding a ZC1 kinase polypeptide having the complete amino acid sequence as set forth in SEQ ID NO:13 or encodes at least 250 contiguous amino acids of the amino acid sequence set forth in SEQ ID NO:13 and having kinase activity.

51. An isolated, enriched or purified ZC1 kinase polypeptide having the amino acid sequence set forth in SEQ ID NO:13 or a fragment thereof comprising at least 250 contiguous amino acids of SEQ ID NO:13 and having kinase activity.

52. An isolated, enriched or purified ZC1 kinase polypeptide having the amino acid sequence set forth in SEQ ID NO:13 except that it lacks one or more of the domains defined by amino acid segments 1-22, 290-526, 527-640, 641-896, or 897-1239 of SEQ ID NO:13 and having kinase activity.

53. The kinase polypeptide molecule of claim 51 or claim 52 wherein said polypeptide is isolated, enriched or purified from a mammal.

54. The kinase polypeptide molecule of claim 53 wherein said mammal is a human.

55. An antibody or antibody fragment having specific binding affinity to a ZC1 kinase polypeptide having the complete amino acid sequence set forth in SEQ ID NO:13 or a fragment thereof comprising at least 250 contiguous amino acids of SEQ ID NO:13 and having kinase activity or having the amino acid sequence set forth in SEQ ID NO:13 except that it lacks one or more of the domains defined by amino acid segments 1-22, 290-526, 527-640, 641-896, or 897-1239 of SEQ ID NO:13.

56. A hybridoma which produces an antibody having specific binding affinity to a ZC1 kinase polypeptide having the amino acid sequence set forth in SEQ ID NO: 13 or a fragment thereof comprising at least 250 contiguous amino acids of SEQ ID NO :13 and having kinase activity, or having the amino acid sequence set forth in SEQ ID NO: 13 except that it lacks one or more of the domains defined by amino acid segments 1-22, 290-526, 527-640, 641-896, or 897-1239 of SEQ ID NO:13.



57. A method for identifying a substance that modulates kinase activity comprising the steps of:

- (a) contacting a ZC1 kinase polypeptide having the amino acid sequence set forth in SEQ ID NO:13 or a fragment thereof comprising at least 250 contiguous amino acids of SEQ ID NO:13 and having kinase activity, or having the amino acid sequence set forth in SEQ ID NO:13 except that it lacks one or more of the domains defined by amino acid segments 1-22, 290-526, 527-640, 641-896, or 897-1239 of SEQ ID NO:13;
- (b) measuring the activity of said polypeptide; and
- (c) determining whether said substance modulates the activity of said polypeptide.

58. A method for identifying a substance that modulates kinase activity comprising the steps of:

- (a) expressing a ZC1 kinase polypeptide having the amino acid sequence set forth in SEQ ID NO:13 or a fragment thereof comprising at least 250 contiguous amino acids of SEQ ID NO:13 and having kinase activity, or having the amino acid sequence set forth in SEQ ID NO:13 except that it lacks one or more of the domains defined by amino acid segments 1-22, 290-526, 527-640, 641-896, or 897-1239 of SEQ ID NO:13;
- (b) adding a test substance to said cell; and
- (c) monitoring a change in cell phenotype or the interaction between said polypeptide and a natural binding partner.

59. A method for detection of a ZC1 kinase polypeptide in a sample as a diagnostic tool for a disease or disorder wherein said method comprises:

- (a) contacting said sample with a nucleic acid probe which specifically hybridizes, under hybridization

conditions which are at least as stringent as hybridization in 50% formamide, 5X SSC, 50mM NaH<sub>2</sub>PO<sub>4</sub>, pH6.8, 0.5% SDS, 0.1 mg/ml sonicated salmon sperm DNA and 5X Denhart solution at 42°C; overnight washing with 2X SSC, 0.1% SDS at 45°C; and washing with 0.2X SSC, 0.1% SDS at 45°C, to a ZC1 kinase nucleic acid target region that,

encodes the complete amino acid sequence as set forth in SEQ ID NO:13 or the complement of all of the nucleotides thereof, encodes at least 250 contiguous amino acids of the amino acid sequence set forth in SEQ ID NO:13 and having kinase activity or the complement of all of the nucleotides thereof, or encodes a polypeptide having kinase activity comprising the amino acid sequence set forth in SEQ ID NO:13 except that it lacks one or more of the domains defined by amino acid segments 1-22, 290-526, 527-640, 641-896, or 897-1239 of SEQ ID NO:13 or the complement of all of the nucleotides thereof; and

(b) detecting the presence of the probe:target region hybrid as an indication of said disease.

60. The method of claim 59 wherein said disease or disorder is selected from the group consisting of immune-related diseases and disorders, organ transplantation, myocardial infarction, cardiovascular disease, stroke, renal failure, oxidative stress-related neurodegenerative disorders and cancer.

61. A method for detection of a ZC1 kinase polypeptide in a sample as a diagnostic tool for a disease or disorder wherein said method comprises:

(a) comparing a nucleic acid target region encoding said ZC1 kinase polypeptide in a sample, said ZC1 kinase polypeptide having an amino acid sequence as set forth in SEQ ID NO:13, at least 250 contiguous amino acids thereof

and having kinase activity, or the amino acid sequence set forth in SEQ ID NO:13 except that it lacks one or more of the domains defined by amino acid segments 1-22, 290-526, 527-640, 641-896, or 897-1239 of SEQ ID NO:13, with a control nucleic acid target region encoding said ZC1 kinase polypeptide; and

(b) detecting differences in sequence or amount between said target region and said control target region as an indication of said disease or disorder.

62. The method of claim 61 wherein said disease or disorder is selected from the group consisting of immune-related diseases and disorders, organ transplantation, myocardial infarction, cardiovascular disease, stroke, renal failure, oxidative stress-related neurodegenerative disorders and cancer.

63. A method for treating a disease or disorder by administering to a patient in need of such treatment a substance that modulates the activity of a ZC1 kinase having an amino acid sequence as set forth in SEQ ID NO:13, a fragment thereof comprising at least 250 contiguous amino acids of SEQ ID NO :13 and having kinase activity or having the amino acid sequence set forth in SEQ ID NO:13 except that it lacks one or more of the domains defined by amino acid segments 1-22, 290-526, 527-640, 641-896, or 897-1239 of SEQ ID NO:13.

64. The method of claim 63 wherein said disease or disorder is selected from the group consisting of immune-related diseases and disorders, organ transplantation, myocardial infarction, cardiovascular disease, stroke, renal failure, oxidative stress-related neurodegenerative disorders and cancer.

65. The method of claim 63 or claim 64 wherein said substance modulates kinase activity *in vitro*.

66. The method of claim 65, wherein said substance is a kinase inhibitor.

67. An isolated, enriched or purified nucleic acid molecule encoding a ZC2 kinase polypeptide said nucleic acid molecule comprising a nucleotide sequence that:

(a) encodes the complete amino acid sequence as set forth in SEQ ID NO:14;

(b) is the complement of all of the nucleotide sequence of (a)

(c) encodes a polypeptide having kinase activity comprising the amino acid sequence set forth in SEQ ID NO:14 except that it lacks one or more of the domains defined by amino acid segments 256-442, 443-626, 627-954 or 955-1297 of SEQ ID NO:14;

(d) is the complement of all of the nucleotide sequence of (c).

68. The nucleic acid molecule of claim 67 wherein said nucleic acid molecule is isolated, enriched or purified from a mammal.

69. The nucleic acid molecule of claim 68 wherein said mammal is a human.

70. The nucleic acid molecule of any of claims 67 to 69, further comprising a vector or promoter effective to initiate transcription in a host cell.

71. A nucleic acid probe for the detection of

nucleic acid encoding a ZC2 kinase polypeptide in a sample, said probe specifically hybridizing to a nucleic acid molecule that encodes the complete amino acid sequence as set forth in SEQ ID NO:14.

72. A recombinant cell comprising a nucleic acid molecule encoding a ZC2 kinase polypeptide having the complete amino acid sequence as set forth in SEQ ID NO:14.

73. An isolated, enriched or purified ZC2 kinase polypeptide having the amino acid sequence set forth in SEQ ID NO:14.

74. An isolated, enriched or purified ZC2 kinase polypeptide having the amino acid sequence set forth in SEQ ID NO:14 except that it lacks one or more of the domains defined by amino acid segments 256-442, 443-626, 627-954 or 955-1297 of SEQ ID NO:14 and having kinase activity.

75. The kinase polypeptide molecule of claim 73 or claim 74 wherein said polypeptide is isolated, enriched or purified from a mammal.

76. The kinase polypeptide molecule of claim 75 wherein said mammal is a human.

77. An antibody or antibody fragment having specific binding affinity to a ZC2 kinase polypeptide having the complete amino acid sequence set forth in SEQ ID NO:14, or having the amino acid sequence set forth in SEQ ID NO:14 except that it lacks one or more of the domains defined by amino acid segments 256-442, 443-626,

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627-954 or 955-1297 of SEQ ID NO:14.

78. A hybridoma which produces an antibody having specific binding affinity to a ZC2 kinase polypeptide having the complete amino acid sequence set forth in SEQ ID NO:14, or having the amino acid sequence set forth in SEQ ID NO:14 except that it lacks one or more of the domains defined by amino acid segments 256-442, 443-626, 627-954 or 955-1297 of SEQ ID NO:14.

79. A method for identifying a substance that modulates kinase activity comprising the steps of:  
(a) contacting a ZC2 kinase polypeptide having the complete amino acid sequence set forth in SEQ ID NO:14, or having the amino acid sequence set forth in SEQ ID NO:14 except that it lacks one or more of the domains defined by amino acid segments 256-442, 443-626, 627-954 or 955-1297 of SEQ ID NO:14 with a test substance;  
(b) measuring the activity of said polypeptide; and  
(c) determining whether said substance modulates the activity of said polypeptide.

80. A method for identifying a substance that modulates kinase activity comprising the steps of:  
(a) expressing a ZC2 kinase polypeptide having the complete amino acid sequence set forth in SEQ ID NO:14, or having the amino acid sequence set forth in SEQ ID NO:14 except that it lacks one or more of the domains defined by amino acid segments 256-442, 443-626, 627-954 or 955-1297 of SEQ ID NO:14;  
(b) adding a test substance to said cell; and  
(c) monitoring a change in cell phenotype or the interaction between said polypeptide and a natural binding partner.

AMENDED SHEET

81. A method for detection of a ZC2 kinase polypeptide in a sample as a diagnostic tool for a disease or disorder wherein said method comprises:

(a) contacting said sample with a nucleic acid probe which specifically hybridizes, under hybridization conditions which are at least as stringent as hybridization in 50% formamide, 5X SSC, 50mM  $\text{NaH}_2\text{PO}_4$ , pH6.8, 0.5% SDS, 0.1 mg/ml sonicated salmon sperm DNA and 5X Denhart solution at 42°C; overnight washing with 2X SSC, 0.1% SDS at 45°C; and washing with 0.2X SSC, 0.1% SDS at 45°C to a ZC2 kinase nucleic acid target region that,

encodes the complete amino acid sequence as set forth in SEQ ID NO:14 or is the complement of all of the nucleotides thereof, or encodes a polypeptide having kinase activity comprising the amino acid sequence set forth in SEQ ID NO:14 except that it lacks one or more of the domains defined by amino acid segments 256-442, 443-626, 627-954 or 955-1297 of SEQ ID NO:14 or is the complement of all of the nucleotides thereof; and

(b) detecting the presence of the probe:target region hybrid as an indication of said disease.

82. The method of claim 81 wherein said disease or disorder is selected from the group consisting of immune-related diseases and disorders, organ transplantation, myocardial infarction, cardiovascular disease, stroke, renal failure, oxidative stress-related neurodegenerative disorders and cancer.

83. A method for detection of a ZC2 kinase polypeptide in a sample as a diagnostic tool for a disease or disorder wherein said method comprises:

(a) comparing a nucleic acid target region encoding

said ZC2 kinase polypeptide in a sample, said kinase polypeptide having an amino acid sequence as set forth in SEQ ID NO:14, or the amino acid sequence as set forth in SEQ ID NO:14 except that it lacks one or more of the domains defined by amino acid segments 256-442, 443-626, 627-954 or 955-1297 of SEQ ID NO:14, with a control nucleic acid target region encoding said ZC2 kinase polypeptide; and

(b) detecting differences in sequence or amount between said target region and said control target region as an indication of said disease or disorder.

84. The method of claim 83 wherein said disease or disorder is selected from the group consisting of immune-related diseases and disorders, organ transplantation, myocardial infarction, cardiovascular disease, stroke, renal failure, oxidative stress-related neurodegenerative disorders and cancer.

85. A method for treating a disease or disorder by administering to a patient in need of such treatment a substance that modulates the activity of a ZC2 kinase having an amino acid sequence as set forth in SEQ ID NO:14, or the amino acid sequence as set forth in SEQ ID NO:14 except that it lacks one or more of the domains defined by amino acid segments 256-442, 443-626, 627-954 or 955-1297 of SEQ ID NO:14.

86. The method of claim 85 wherein said disease or disorder is selected from the group consisting of immune-related diseases and disorders, organ transplantation, myocardial infarction, cardiovascular disease, stroke, renal failure, oxidative stress-related neurodegenerative disorders and cancer.



87. The method of claim 85 or claim 86 wherein said substance modulates kinase activity *in vitro*.

88. The method of claim 87, wherein said substance is a kinase inhibitor.

89. An isolated, enriched or purified nucleic acid molecule encoding a ZC3 kinase polypeptide said nucleic acid molecule comprising a nucleotide sequence that:

(a) encodes the complete amino acid sequence as set forth in SEQ ID NO:15;

(b) is the complement of all of the nucleotide sequence of (a);

(c) encodes at least 250 contiguous amino acids of the amino acid sequence set forth in SEQ ID NO:15 and having kinase activity;

(d) is the complement of all of the nucleotide sequence of (c);

(e) encodes a polypeptide having kinase activity comprising the amino acid sequence set forth in SEQ ID NO:15 except that it lacks one or more of the domains defined by amino acid segments 256-476, 477-680, 681-983, or 984-1326 of SEQ ID NO:15;

(f) is the complement of all of the nucleotide sequence of (e).

90. The nucleic acid molecule of claim 89 wherein said nucleic acid molecule is isolated, enriched or purified from a mammal.

91. The nucleic acid molecule of claim 90 wherein said mammal is a human.

92. The nucleic acid molecule of any of claims 89 to 91, further comprising a vector or promoter effective to initiate transcription in a host cell.

93. A nucleic acid probe for the detection of nucleic acid encoding a ZC3 kinase polypeptide in a sample, said probe specifically hybridizing to a nucleic acid molecule that encodes the complete amino acid sequence as set forth in SEQ ID NO:15 or encodes at least 250 contiguous amino acids of the amino acid sequence set forth in SEQ ID NO:15 and having kinase activity.

94. A recombinant cell comprising a nucleic acid molecule encoding a ZC3 kinase polypeptide having the complete amino acid sequence as set forth in SEQ ID NO:15 or encodes at least 250 contiguous amino acids of the amino acid sequence set forth in SEQ ID NO:15 and having kinase activity.

95. An isolated, enriched or purified ZC3 kinase polypeptide having the amino acid sequence set forth in SEQ ID NO:15 or a fragment thereof comprising at least 250 contiguous amino acids of SEQ ID NO:15 and having kinase activity.

96. An isolated, enriched or purified ZC3 kinase polypeptide having the amino acid sequence set forth in SEQ ID NO:15 except that it lacks one or more of the domains defined by amino acid segments 256-476, 477-680, 681-983, or 984-1326 of SEQ ID NO:15 and having kinase activity.

97. The kinase polypeptide molecule of claim 95 or claim 96 wherein said polypeptide is isolated, enriched

or purified from a mammal.

98. The kinase polypeptide molecule of claim 97 wherein said mammal is a human.

99. An antibody or antibody fragment having specific binding affinity to a ZC3 kinase polypeptide having the complete amino acid sequence set forth in SEQ ID NO:15, a fragment thereof comprising at least 250 contiguous amino acids of SEQ ID NO:15 and having kinase activity or having the amino acid sequence set forth in SEQ ID NO:15 except that it lacks one or more of the domains defined by amino acid segments 256-476, 477-680, 681-983, or 984-1326 of SEQ ID NO:15.

100. A hybridoma which produces an antibody having specific binding affinity to a ZC3 kinase polypeptide having the complete amino acid sequence set forth in SEQ ID NO:15, a fragment thereof comprising at least 250 contiguous amino acids of SEQ ID NO:15 and having kinase activity or having the amino acid sequence set forth in SEQ ID NO:15 except that it lacks one or more of the domains defined by amino acid segments 256-476, 477-680, 681-983, or 984-1326 of SEQ ID NO:15.

101. A method for identifying a substance that modulates kinase activity comprising the steps of:

(a) contacting a ZC3 kinase polypeptide having the complete amino acid sequence set forth in SEQ ID NO:15, a fragment thereof comprising at least 250 contiguous amino acids of SEQ ID NO:15 and having kinase activity or having the amino acid sequence set forth in SEQ ID NO:15 except that it lacks one or more of the domains defined by amino acid segments 256-476, 477-680, 681-983, or 984-

1326 of SEQ ID NO:15 with a test substance;

- (b) measuring the activity of said polypeptide; and
- (c) determining whether said substance modulates the activity of said polypeptide.

102. A method for identifying a substance that modulates kinase activity comprising the steps of:

- (a) expressing a ZC3 kinase polypeptide having the complete amino acid sequence set forth in SEQ ID NO:15, a fragment thereof comprising at least 250 contiguous amino acids of SEQ ID NO:15 and having kinase activity or having the amino acid sequence set forth in SEQ ID NO:15 except that it lacks one or more of the domains defined by amino acid segments 256-476, 477-680, 681-983, or 984-1326 of SEQ ID NO:15;

- (b) adding a test substance to said cell; and
- (c) monitoring a change in cell phenotype or the interaction between said polypeptide and a natural binding partner.

103. A method for detection of a ZC3 kinase polypeptide in a sample as a diagnostic tool for a disease or disorder wherein said method comprises:

- (a) contacting said sample with a nucleic acid probe which specifically hybridizes, under hybridization conditions which are at least as stringent as hybridization in 50% formamide, 5X SSC, 50mM NaH<sub>2</sub>PO<sub>4</sub>, pH6.8, 0.5% SDS, 0.1 mg/ml sonicated salmon sperm DNA and 5X Denhart solution at 42°C; overnight washing with 2X SSC, 0.1% SDS at 45°C; and washing with 0.2X SSC, 0.1% SDS at 45°C to a ZC3 kinase nucleic acid target region that, encodes the complete amino acid sequence as set forth in SEQ ID NO:15 or is the complement of all of the nucleotides thereof, encodes at least 250 contiguous

amino acids of the amino acid sequence set forth in SEQ ID NO:15 and having kinase activity or the complement of all of the nucleotides thereof, or encodes a polypeptide having kinase activity comprising the amino acid sequence set forth in SEQ ID NO:15 except that it lacks one or more of the domains defined by amino acid segments 256-476, 477-680, 681-983, or 984-1326 of SEQ ID NO:15 or is the complement of all of the nucleotides thereof; and

(b) detecting the presence of the probe:target region hybrid as an indication of said disease.

104. The method of claim 103 wherein said disease or disorder is selected from the group consisting of immune-related diseases and disorders, organ transplantation, myocardial infarction, cardiovascular disease, stroke, renal failure, oxidative stress-related neurodegenerative disorders and cancer.

105. A method for detection of a ZC3 kinase polypeptide in a sample as a diagnostic tool for a disease or disorder wherein said method comprises:

(a) comparing a nucleic acid target region encoding said ZC3 kinase polypeptide in a sample, said kinase polypeptide having an amino acid sequence as set forth in SEQ ID NO:15, at least 250 contiguous amino acids thereof and having kinase activity, or the amino acid sequence as set forth in SEQ ID NO:15 except that it lacks one or more of the domains defined by amino acid segments 256-476, 477-680, 681-983, or 984-1326 of SEQ ID NO:15, with a control nucleic acid target region encoding said ZC3 kinase polypeptide; and

(b) detecting differences in sequence or amount between said target region and said control target region as an indication of said disease or disorder.

106. The method of claim 105 wherein said disease or disorder is selected from the group consisting of immune-related diseases and disorders, organ transplantation, myocardial infarction, cardiovascular disease, stroke, renal failure, oxidative stress-related neurodegenerative disorders and cancer.

107. A method for treating a disease or disorder by administering to a patient in need of such treatment a substance that modulates the activity of a ZC3 kinase having an amino acid sequence as set forth in SEQ ID NO:15, at least 25 contiguous amino acids thereof and having kinase activity, or the amino acid sequence as set forth in SEQ ID NO:15 except that it lacks one or more of the domains defined by amino acid segments 256-476, 477-680, 681-983, or 984-1326 of SEQ ID NO:15.

108. The method of claim 107 wherein said disease or disorder is selected from the group consisting of immune-related diseases and disorders, organ transplantation, myocardial infarction, cardiovascular disease, stroke, renal failure, oxidative stress-related neurodegenerative disorders and cancer.

109. The method of claim 107 or claim 108 wherein said substance modulates kinase activity in vitro.

110. The method of claim 109, wherein said substance is a kinase inhibitor.

111. An isolated, enriched or purified nucleic acid molecule encoding a KHS2 kinase polypeptide said nucleic acid molecule comprising a nucleotide sequence

that:

(a) encodes the complete amino acid sequence as set forth in SEQ ID NO:18;

(b) is the complement of all of the nucleotide sequence of (a)

(c) encodes a polypeptide having kinase activity comprising the amino acid sequence set forth in SEQ ID NO:18 except that it lacks one or more of the domains defined by amino acid segments 274-346, 347-534, or 535-894 of SEQ ID NO:18;

(d) is the complement of all of the nucleotide sequence of (c).

112. The nucleic acid molecule of claim 111 wherein said nucleic acid molecule is isolated, enriched or purified from a mammal.

113. The nucleic acid molecule of claim 112 wherein said mammal is a human.

114. The nucleic acid molecule of any of claims 111 to 113, further comprising a vector or promoter effective to initiate transcription in a host cell.

115. A nucleic acid probe for the detection of nucleic acid encoding a KHS2 kinase polypeptide in a sample, said probe specifically hybridizing to a nucleic acid molecule that encodes the complete amino acid sequence as set forth in SEQ ID NO:18.

116. A recombinant cell comprising a nucleic acid molecule encoding a KHS2 kinase polypeptide having the complete amino acid sequence as set forth in SEQ ID NO:18.

117. An isolated, enriched or purified KHS2 kinase polypeptide having the amino acid sequence set forth in SEQ ID NO:18.

118. An isolated, enriched or purified KHS2 kinase polypeptide having the amino acid sequence set forth in SEQ ID NO:18 except that it lacks one or more of the domains defined by amino acid segments 274-346, 347-534, or 535-894 of SEQ ID NO:18 and having kinase activity.

119. The kinase polypeptide molecule of claim 117 or claim 118 wherein said polypeptide is isolated, enriched or purified from a mammal.

120. The kinase polypeptide molecule of claim 119 wherein said mammal is a human.

121. An antibody or antibody fragment having specific binding affinity to a KHS2 kinase polypeptide having the complete amino acid sequence set forth in SEQ ID NO:18, or having the amino acid sequence set forth in SEQ ID NO:18 except that it lacks one or more of the domains defined by amino acid segments 274-346, 347-534, or 535-894 of SEQ ID NO:18.

122. A hybridoma which produces an antibody having specific binding affinity to a KHS2 kinase polypeptide having the complete amino acid sequence set forth in SEQ ID NO:18, or having the amino acid sequence set forth in SEQ ID NO:18 except that it lacks one or more of the domains defined by amino acid segments 274-346, 347-534, or 535-894 of SEQ ID NO:18.



123. A method for identifying a substance that modulates kinase activity comprising the steps of:

- (a) contacting a KHS2 kinase polypeptide having the complete amino acid sequence set forth in SEQ ID NO:18, or having the amino acid sequence set forth in SEQ ID NO:18 except that it lacks one or more of the domains defined by amino acid segments 274-346, 347-534, or 535-894 of SEQ ID NO:18 with a test substance;
- (b) measuring the activity of said polypeptide; and
- (c) determining whether said substance modulates the activity of said polypeptide.

124. A method for identifying a substance that modulates kinase activity comprising the steps of:

- (a) expressing a KHS2 kinase polypeptide having the complete amino acid sequence set forth in SEQ ID NO:18, or having the amino acid sequence set forth in SEQ ID NO:18 except that it lacks one or more of the domains defined by amino acid segments 274-346, 347-534, or 535-894 of SEQ ID NO:18;
- (b) adding a test substance to said cell; and
- (c) monitoring a change in cell phenotype or the interaction between said polypeptide and a natural binding partner.

125. A method for detection of a KHS2 kinase polypeptide in a sample as a diagnostic tool for a disease or disorder wherein said method comprises:

- (a) contacting said sample with a nucleic acid probe which specifically hybridizes, under hybridization conditions which are at least as stringent as hybridization in 50% formamide, 5X SSC, 50mM NaH<sub>2</sub>PO<sub>4</sub>, pH6.8, 0.5% SDS, 0.1 mg/ml sonicated salmon sperm DNA and 5X Denhart solution at 42°C; overnight washing with 2X

SSC, 0.1%SDS at 45°C; and washing with 0.2X SSC, 0.1% SDS at 45°C to a KHS2 kinase nucleic acid target region that, encodes the complete amino acid sequence as set forth in SEQ ID NO:18 or is the complement of all of the nucleotides thereof, or encodes a polypeptide having kinase activity comprising the amino acid sequence set forth in SEQ ID NO:18 except that it lacks one or more of the domains defined by amino acid segments 274-346, 347-534, or 535-894 of SEQ ID NO:18 or is the complement of all of the nucleotides thereof; and

(b) detecting the presence of the probe:target region hybrid as an indication of said disease.

126. The method of claim 125 wherein said disease or disorder is selected from the group consisting of immune-related diseases and disorders, organ transplantation, myocardial infarction, cardiovascular disease, stroke, renal failure, oxidative stress-related neurodegenerative disorders and cancer.

127. A method for detection of a KHS2 kinase polypeptide in a sample as a diagnostic tool for a disease or disorder wherein said method comprises:

- (a) comparing a nucleic acid target region encoding said KHS2 kinase polypeptide in a sample, said kinase polypeptide having an amino acid sequence as set forth in SEQ ID NO:18, or the amino acid sequence as set forth in SEQ ID NO:18 except that it lacks one or more of the domains defined by amino acid segments 274-346, 347-534, or 535-894 of SEQ ID NO:18, with a control nucleic acid target region encoding said KHS2 kinase polypeptide; and
- (b) detecting differences in sequence or amount between said target region and said control target region as an indication of said disease or disorder.

128. The method of claim 127 wherein said disease or disorder is selected from the group consisting of immune-related diseases and disorders, organ transplantation, myocardial infarction, cardiovascular disease, stroke, renal failure, oxidative stress-related neurodegenerative disorders and cancer.

129. A method for treating a disease or disorder by administering to a patient in need of such treatment a substance that modulates the activity of a KHS2 kinase having an amino acid sequence as set forth in SEQ ID NO:18, or the amino acid sequence as set forth in SEQ ID NO:18 except that it lacks one or more of the domains defined by amino acid segments 274-346, 347-534, or 535-894 of SEQ ID NO:18.

130. The method of claim 129 wherein said disease or disorder is selected from the group consisting of immune-related diseases and disorders, organ transplantation, myocardial infarction, cardiovascular disease, stroke, renal failure, oxidative stress-related neurodegenerative disorders and cancer.

131. The method of claim 129 or claim 130 wherein said substance modulates kinase activity *in vitro*.

132. The method of claim 131, wherein said substance is a kinase inhibitor.

133. An isolated, enriched or purified nucleic acid molecule encoding a SULU1 kinase polypeptide said nucleic acid molecule comprising a nucleotide sequence that:

(a) encodes the complete amino acid sequence as set

forth in SEQ ID NO:22;

(b) is the complement of all of the nucleotide sequence of (a);

(c) encodes at least 200 contiguous amino acids of the amino acid sequence set forth in SEQ ID NO:22 and having kinase activity;

(d) is the complement of all of the nucleotide sequence of (c);

(e) encodes a polypeptide having kinase activity comprising the amino acid sequence set forth in SEQ ID NO:22 except that it lacks one or more of the domains defined by amino acid segments 1-21, 278-427, 428-637, 638-751, or 752-898 of SEQ ID NO:22;

(f) is the complement of all of the nucleotide sequence of (e).

134. The nucleic acid molecule of claim 133 wherein said nucleic acid molecule is isolated, enriched or purified from a mammal.

135. The nucleic acid molecule of claim 134 wherein said mammal is a human.

136. The nucleic acid molecule of any of claims 133 to 135, further comprising a vector or promoter effective to initiate transcription in a host cell.

137. A nucleic acid probe for the detection of nucleic acid encoding a SULU1 kinase polypeptide in a sample, said probe specifically hybridizing to a nucleic acid molecule that encodes the complete amino acid sequence as set forth in SEQ ID NO:22 or encodes at least 200 contiguous amino acids of the amino acid sequence set forth in SEQ ID NO:22 and having kinase activity.

138. A recombinant cell comprising a nucleic acid molecule encoding a SULU1 kinase polypeptide having the complete amino acid sequence as set forth in SEQ ID NO:22 or encodes at least 200 contiguous amino acids of the amino acid sequence set forth in SEQ ID NO:22 and having kinase activity.

139. An isolated, enriched or purified SULU1 kinase polypeptide having the amino acid sequence set forth in SEQ ID NO:22 or a fragment thereof comprising at least 200 contiguous amino acids of SEQ ID NO:22 and having kinase activity.

140. An isolated, enriched or purified SULU1 kinase polypeptide having the amino acid sequence set forth in SEQ ID NO:22 except that it lacks one or more of the domains defined by amino acid segments 1-21, 278-427, 428-637, 638-751, or 752-898 of SEQ ID NO:22 and having kinase activity.

141. The kinase polypeptide molecule of claim 139 or claim 140 wherein said polypeptide is isolated, enriched or purified from a mammal.

142. The kinase polypeptide molecule of claim 141 wherein said mammal is a human.

143. An antibody or antibody fragment having specific binding affinity to a SULU1 kinase polypeptide having the complete amino acid sequence set forth in SEQ ID NO:22, a fragment thereof comprising at least 200 contiguous amino acids of SEQ ID NO:22 and having kinase activity or having the amino acid sequence set forth in

SEQ ID NO:22 except that it lacks one or more of the domains defined by amino acid segments 1-21, 278-427, 428-637, 638-751, or 752-898 of SEQ ID NO:22.

144. A hybridoma which produces an antibody having specific binding affinity to a SULU1 kinase polypeptide having the complete amino acid sequence set forth in SEQ ID NO:22, a fragment thereof comprising at least 200 contiguous amino acids of SEQ ID NO:22 and having kinase activity or having the amino acid sequence set forth in SEQ ID NO:22 except that it lacks one or more of the domains defined by amino acid segments 1-21, 278-427, 428-637, 638-751, or 752-898 of SEQ ID NO:22.

145. A method for identifying a substance that modulates kinase activity comprising the steps of:

- (a) contacting a SULU1 kinase polypeptide having the complete amino acid sequence set forth in SEQ ID NO:22, a fragment thereof comprising at least 200 contiguous amino acids of SEQ ID NO:22 and having kinase activity or having the amino acid sequence set forth in SEQ ID NO:22 except that it lacks one or more of the domains defined by amino acid segments 1-21, 278-427, 428-637, 638-751, or 752-898 of SEQ ID NO:22 with a test substance;
- (b) measuring the activity of said polypeptide; and
- (c) determining whether said substance modulates the activity of said polypeptide.

146. A method for identifying a substance that modulates kinase activity comprising the steps of:

- (a) expressing a SULU1 kinase polypeptide having the complete amino acid sequence set forth in SEQ ID NO:22, a fragment thereof comprising at least 200

contiguous amino acids of SEQ ID NO:22 and having kinase activity or having the amino acid sequence set forth in SEQ ID NO:22 except that it lacks one or more of the domains defined by amino acid segments 1-21, 278-427, 428-637, 638-751, or 752-898 of SEQ ID NO:22;

- (b) adding a test substance to said cell; and
- (c) monitoring a change in cell phenotype or the interaction between said polypeptide and a natural binding partner.

147. A method for detection of a SULU1 kinase polypeptide in a sample as a diagnostic tool for a disease or disorder wherein said method comprises:

- (a) contacting said sample with a nucleic acid probe which specifically hybridizes, under hybridization conditions which are at least as stringent as hybridization in 50% formamide, 5X SSC, 50mM NaH<sub>2</sub>PO<sub>4</sub>, pH6.8, 0.5% SDS, 0.1 mg/ml sonicated salmon sperm DNA and 5X Denhart solution at 42°C; overnight washing with 2X SSC, 0.1%SDS at 45°C; and washing with 0.2X SSC, 0.1% SDS at 45°C to a SULU1 kinase nucleic acid target region that,

encodes the complete amino acid sequence as set forth in SEQ ID NO:22 or is the complement of all of the nucleotides thereof, encodes at least 200 contiguous amino acids of the amino acid sequence set forth in SEQ ID NO:22 and having kinase activity or the complement of all of the nucleotides thereof, or encodes a polypeptide having kinase activity comprising the amino acid sequence set forth in SEQ ID NO:22 except that it lacks one or more of the domains defined by amino acid segments 1-21, 278-427, 428-637, 638-751, or 752-898 of SEQ ID NO:22 or is the complement of all of the nucleotides thereof; and

- (b) detecting the presence of the probe:target

region hybrid as an indication of said disease.

148. The method of claim 147 wherein said disease or disorder is selected from the group consisting of immune-related diseases and disorders, organ transplantation, myocardial infarction, cardiovascular disease, stroke, renal failure, oxidative stress-related neurodegenerative disorders and cancer.

149. A method for detection of a SULU1 kinase polypeptide in a sample as a diagnostic tool for a disease or disorder wherein said method comprises:

(a) comparing a nucleic acid target region encoding said SULU1 kinase polypeptide in a sample, said kinase polypeptide having an amino acid sequence as set forth in SEQ ID NO:22, at least 200 contiguous amino acids thereof and having kinase activity, or the amino acid sequence as set forth in SEQ ID NO:22 except that it lacks one or more of the domains defined by amino acid segments 1-21, 278-427, 428-637, 638-751, or 752-898 of SEQ ID NO:22, with a control nucleic acid target region encoding said SULU1 kinase polypeptide; and

(b) detecting differences in sequence or amount between said target region and said control target region as an indication of said disease or disorder.

150. The method of claim 149 wherein said disease or disorder is selected from the group consisting of immune-related diseases and disorders, organ transplantation, myocardial infarction, cardiovascular disease, stroke, renal failure, oxidative stress-related neurodegenerative disorders and cancer.

151. A method for treating a disease or disorder by



administering to a patient in need of such treatment a substance that modulates the activity of a SULU1 kinase having an amino acid sequence as set forth in SEQ ID NO:22, at least 25 contiguous amino acids thereof and having kinase activity, or the amino acid sequence as set forth in SEQ ID NO:22 except that it lacks one or more of the domains defined by amino acid segments 1-21, 278-427, 428-637, 638-751, or 752-898 of SEQ ID NO:22.

152. The method of claim 151 wherein said disease or disorder is selected from the group consisting of immune-related diseases and disorders, organ transplantation, myocardial infarction, cardiovascular disease, stroke, renal failure, oxidative stress-related neurodegenerative disorders and cancer.

153. The method of claim 151 or claim 152 wherein said substance modulates kinase activity in vitro.

154. The method of claim 153, wherein said substance is a kinase inhibitor.

155. An isolated, enriched or purified nucleic acid molecule encoding a GEK2 kinase polypeptide said nucleic acid molecule comprising a nucleotide sequence that:

- (a) encodes the complete amino acid sequence as set forth in SEQ ID NO:107;
- (b) is the complement of all of the nucleotide sequence of (a)

156. The nucleic acid molecule of claim 155 wherein said nucleic acid molecule is isolated, enriched or purified from a mammal.

157. The nucleic acid molecule of claim 156 wherein said mammal is a human.

158. The nucleic acid molecule of any of claims 155 to 157, further comprising a vector or promoter effective to initiate transcription in a host cell.

159. A nucleic acid probe for the detection of nucleic acid encoding a GEK2 kinase polypeptide in a sample, said probe specifically hybridizing to a nucleic acid molecule that encodes the complete amino acid sequence as set forth in SEQ ID NO:107.

160. A recombinant cell comprising a nucleic acid molecule encoding a GEK2 kinase polypeptide having the complete amino acid sequence as set forth in SEQ ID NO:107.

161. An isolated, enriched or purified GEK2 kinase polypeptide having the amino acid sequence set forth in SEQ ID NO:107.

162. The kinase polypeptide molecule of claim 161 wherein said polypeptide is isolated, enriched or purified from a mammal.

163. The kinase polypeptide molecule of claim 162 wherein said mammal is a human.

164. An antibody or antibody fragment having specific binding affinity to a GEK2 kinase polypeptide having the complete amino acid sequence set forth in SEQ ID NO:107.

165. A hybridoma which produces an antibody having specific binding affinity to a GEK2 kinase polypeptide having the complete amino acid sequence set forth in SEQ ID NO:107.

166. A method for identifying a substance that modulates kinase activity comprising the steps of:

- (a) contacting a GEK2 kinase polypeptide having the complete amino acid sequence set forth in SEQ ID NO:107 with a test substance;
- (b) measuring the activity of said polypeptide; and
- (c) determining whether said substance modulates the activity of said polypeptide.

167. A method for identifying a substance that modulates kinase activity comprising the steps of:

- (a) expressing a GEK2 kinase polypeptide having the complete amino acid sequence set forth in SEQ ID NO:107;
- (b) adding a test substance to said cell; and
- (c) monitoring a change in cell phenotype or the interaction between said polypeptide and a natural binding partner.

168. A method for detection of a GEK2 kinase polypeptide in a sample as a diagnostic tool for a disease or disorder wherein said method comprises:

- (a) contacting said sample with a nucleic acid probe which specifically hybridizes, under hybridization conditions which are at least as stringent as hybridization in 50% formamide, 5X SSC, 50mM  $\text{NaH}_2\text{PO}_4$ , pH6.8, 0.5% SDS, 0.1 mg/ml sonicated salmon sperm DNA and 5X Denhart solution at 42°C; overnight washing with 2X SSC, 0.1%SDS at 45°C; and washing with 0.2X SSC, 0.1% SDS

at 45°C to a GEK2 kinase nucleic acid target region that, encodes the complete amino acid sequence as set forth in SEQ ID NO:107 or is the complement of all of the nucleotides thereof, and

(b) detecting the presence of the probe:target region hybrid as an indication of said disease.

169. The method of claim 15 wherein said disease or disorder is selected from the group consisting of immune-related diseases and disorders, organ transplantation, myocardial infarction, cardiovascular disease, stroke, renal failure, oxidative stress-related neurodegenerative disorders and cancer.

170. A method for detection of a GEK2 kinase polypeptide in a sample as a diagnostic tool for a disease or disorder wherein said method comprises:

(a) comparing a nucleic acid target region encoding said GEK2 kinase polypeptide in a sample, said kinase polypeptide having an amino acid sequence as set forth in SEQ ID NO:107, with a control nucleic acid target region encoding said GEK2 kinase polypeptide; and

(b) detecting differences in sequence or amount between said target region and said control target region as an indication of said disease or disorder.

171. The method of claim 170 wherein said disease or disorder is selected from the group consisting of immune-related diseases and disorders, organ transplantation, myocardial infarction, cardiovascular disease, stroke, renal failure, oxidative stress-related neurodegenerative disorders and cancer.

172. A method for treating a disease or disorder by

administering to a patient in need of such treatment a substance that modulates the activity of a GEK2 kinase having an amino acid sequence as set forth in SEQ ID NO:107.

173. The method of claim 172 wherein said disease or disorder is selected from the group consisting of immune-related diseases and disorders, organ transplantation, myocardial infarction, cardiovascular disease, stroke, renal failure, oxidative stress-related neurodegenerative disorders and cancer.

174. The method of claim 172 or claim 173 wherein said substance modulates kinase activity *in vitro*.

175. The method of claim 174, wherein said substance is a kinase inhibitor.

176. An isolated, enriched or purified nucleic acid molecule encoding a PAK4 kinase polypeptide said nucleic acid molecule comprising a nucleotide sequence that:

(a) encodes the complete amino acid sequence as set forth in SEQ ID NO:29;

(b) is the complement of all of the nucleotide sequence of (a);

(c) encodes at least 200 contiguous amino acids of the amino acid sequence set forth in SEQ ID NO:29 and having kinase activity;

(d) is the complement of all of the nucleotide sequence of (c);

(e) encodes a polypeptide having kinase activity comprising the amino acid sequence set forth in SEQ ID NO:29 except that it lacks one or more of the domains

defined by amino acid segments 1-51, 52-224, 225-393, or 659-681 of SEQ ID NO:29;

(f) is the complement of all of the nucleotide sequence of (e).

177. The nucleic acid molecule of claim 176 wherein said nucleic acid molecule is isolated, enriched or purified from a mammal.

178. The nucleic acid molecule of claim 177 wherein said mammal is a human.

179. The nucleic acid molecule of any of claims 176 to 178, further comprising a vector or promoter effective to initiate transcription in a host cell.

180. A nucleic acid probe for the detection of nucleic acid encoding a PAK4 kinase polypeptide in a sample, said probe specifically hybridizing to a nucleic acid molecule that encodes the complete amino acid sequence as set forth in SEQ ID NO:29 or encodes at least 200 contiguous amino acids of the amino acid sequence set forth in SEQ ID NO:29 and having kinase activity.

181. A recombinant cell comprising a nucleic acid molecule encoding a PAK4 kinase polypeptide having the complete amino acid sequence as set forth in SEQ ID NO:29 or encodes at least 200 contiguous amino acids of the amino acid sequence set forth in SEQ ID NO:29 and having kinase activity.

182. An isolated, enriched or purified PAK4 kinase polypeptide having the amino acid sequence set forth in SEQ ID NO:29 or a fragment thereof comprising at least

200 contiguous amino acids of SEQ ID NO:29 and having kinase activity.

183. An isolated, enriched or purified PAK4 kinase polypeptide having the amino acid sequence set forth in SEQ ID NO:29 except that it lacks one or more of the domains defined by amino acid segments 1-51, 52-224, 225-393, or 659-681 of SEQ ID NO:29 having kinase activity.

184. The kinase polypeptide molecule of claim 182 or claim 183 wherein said polypeptide is isolated, enriched or purified from a mammal.

185. The kinase polypeptide molecule of claim 184 wherein said mammal is a human.

186. An antibody or antibody fragment having specific binding affinity to a PAK4 kinase polypeptide having the complete amino acid sequence set forth in SEQ ID NO:29, a fragment thereof comprising at least 200 contiguous amino acids of SEQ ID NO:29 and having kinase activity or having the amino acid sequence set forth in SEQ ID NO:29 except that it lacks one or more of the domains defined by amino acid segments 1-51, 52-224, 225-393, or 659-681 of SEQ ID NO:29.

187. A hybridoma which produces an antibody having specific binding affinity to a PAK4 kinase polypeptide having the complete amino acid sequence set forth in SEQ ID NO:29, a fragment thereof comprising at least 200 contiguous amino acids of SEQ ID NO:29 and having kinase activity or having the amino acid sequence set forth in SEQ ID NO:29 except that it lacks one or more of the domains defined by amino acid segments 1-51, 52-224, 225-

393, or 659-681 of SEQ ID NO:29.

188. A method for identifying a substance that modulates kinase activity comprising the steps of:

- (a) contacting a PAK4 kinase polypeptide having the complete amino acid sequence set forth in SEQ ID NO:29, a fragment thereof comprising at least 200 contiguous amino acids of SEQ ID NO:29 and having kinase activity or having the amino acid sequence set forth in SEQ ID NO:29 except that it lacks one or more of the domains defined by amino acid segments 1-51, 52-224, 225-393, or 659-681 of SEQ ID NO:29 with a test substance;
- (b) measuring the activity of said polypeptide; and
- (c) determining whether said substance modulates the activity of said polypeptide.

189. A method for identifying a substance that modulates kinase activity comprising the steps of:

- (a) expressing a PAK4 kinase polypeptide having the complete amino acid sequence set forth in SEQ ID NO:29, a fragment thereof comprising at least 200 contiguous amino acids of SEQ ID NO:29 and having kinase activity or having the amino acid sequence set forth in SEQ ID NO:29 except that it lacks one or more of the domains defined by amino acid segments 1-51, 52-224, 225-393, or 659-681 of SEQ ID NO:29;
- (b) adding a test substance to said cell; and
- (c) monitoring a change in cell phenotype or the interaction between said polypeptide and a natural binding partner.

190. A method for detection of a PAK4 kinase polypeptide in a sample as a diagnostic tool for a disease or disorder wherein said method comprises:



(a) contacting said sample with a nucleic acid probe which specifically hybridizes, under hybridization conditions which are at least as stringent as hybridization in 50% formamide, 5X SSC, 50mM NaH<sub>2</sub>PO<sub>4</sub>, pH6.8, 0.5% SDS, 0.1 mg/ml sonicated salmon sperm DNA and 5X Denhart solution at 42°C; overnight washing with 2X SSC, 0.1% SDS at 45°C; and washing with 0.2X SSC, 0.1% SDS at 45°C to a PAK4 kinase nucleic acid target region that,

encodes the complete amino acid sequence as set forth in SEQ ID NO:29 or is the complement of all of the nucleotides thereof, encodes at least 200 contiguous amino acids of the amino acid sequence set forth in SEQ ID NO:29 and having kinase activity or the complement of all of the nucleotides thereof, or encodes a polypeptide having kinase activity comprising the amino acid sequence set forth in SEQ ID NO:29 except that it lacks one or more of the domains defined by amino acid segments 1-51, 52-224, 225-393, or 659-681 of SEQ ID NO:29 or is the complement of all of the nucleotides thereof; and

(b) detecting the presence of the probe:target region hybrid as an indication of said disease.

191. The method of claim 190 wherein said disease or disorder is selected from the group consisting of immune-related diseases and disorders, organ transplantation, myocardial infarction, cardiovascular disease, stroke, renal failure, oxidative stress-related neurodegenerative disorders and cancer.

192. A method for detection of a PAK4 kinase polypeptide in a sample as a diagnostic tool for a disease or disorder wherein said method comprises:

(a) comparing a nucleic acid target region encoding said PAK4 kinase polypeptide in a sample, said kinase

polypeptide having an amino acid sequence as set forth in SEQ ID NO:29, at least 200 contiguous amino acids thereof and having kinase activity, or the amino acid sequence as set forth in SEQ ID NO:29 except that it lacks one or more of the domains defined by amino acid segments 1-51, 52-224, 225-393, or 659-681 of SEQ ID NO:29, with a control nucleic acid target region encoding said PAK4 kinase polypeptide; and

(b) detecting differences in sequence or amount between said target region and said control target region as an indication of said disease or disorder.

193. The method of claim 192 wherein said disease or disorder is selected from the group consisting of immune-related diseases and disorders, organ transplantation, myocardial infarction, cardiovascular disease, stroke, renal failure, oxidative stress-related neurodegenerative disorders and cancer.

194. A method for treating a disease or disorder by administering to a patient in need of such treatment a substance that modulates the activity of a PAK4 kinase having an amino acid sequence as set forth in SEQ ID NO:29, at least 25 contiguous amino acids thereof and having kinase activity, or the amino acid sequence as set forth in SEQ ID NO:29 except that it lacks one or more of the domains defined by amino acid segments 1-51, 52-224, 225-393, or 659-681 of SEQ ID NO:29.

195. The method of claim 194 wherein said disease or disorder is selected from the group consisting of immune-related diseases and disorders, organ transplantation, myocardial infarction, cardiovascular disease, stroke, renal failure, oxidative stress-related neurodegenerative

disorders and cancer.

196. The method of claim 194 or claim 195 wherein said substance modulates kinase activity *in vitro*.

197. The method of claim 196, wherein said substance is a kinase inhibitor.

198. An isolated, enriched or purified nucleic acid molecule encoding a PAK5 kinase polypeptide said nucleic acid molecule comprising a nucleotide sequence that:

(a) encodes the complete amino acid sequence as set forth in SEQ ID NO:103;

(b) is the complement of all of the nucleotide sequence of (a);

(c) encodes at least 200 contiguous amino acids of the amino acid sequence set forth in SEQ ID NO:103 and having kinase activity;

(d) is the complement of all of the nucleotide sequence of (c);

(e) encodes a polypeptide having kinase activity comprising the amino acid sequence set forth in SEQ ID NO:103 except that it lacks one or more of the domains defined by amino acid segments 1-52, 53-173, 174-307, or 573-591 of SEQ ID NO:103;

(f) is the complement of all of the nucleotide sequence of (e).

199. The nucleic acid molecule of claim 198 wherein said nucleic acid molecule is isolated, enriched or purified from a mammal.

200. The nucleic acid molecule of claim 199

wherein said mammal is a human.

201. The nucleic acid molecule of any of claims 198 to 200, further comprising a vector or promoter effective to initiate transcription in a host cell.

202. A nucleic acid probe for the detection of nucleic acid encoding a PAK5 kinase polypeptide in a sample, said probe specifically hybridizing to a nucleic acid molecule that encodes the complete amino acid sequence as set forth in SEQ ID NO:103 or encodes at least 200 contiguous amino acids of the amino acid sequence set forth in SEQ ID NO:103 and having kinase activity.

203. A recombinant cell comprising a nucleic acid molecule encoding a PAK5 kinase polypeptide having the complete amino acid sequence as set forth in SEQ ID NO:103 or encodes at least 200 contiguous amino acids of the amino acid sequence set forth in SEQ ID NO:103 and having kinase activity.

204. An isolated, enriched or purified PAK5 kinase polypeptide having the amino acid sequence set forth in SEQ ID NO:103 or a fragment thereof comprising at least 200 contiguous amino acids of SEQ ID NO:103 and having kinase activity.

205. An isolated, enriched or purified PAK5 kinase polypeptide having the amino acid sequence set forth in SEQ ID NO:103 except that it lacks one or more of the domains defined by amino acid segments 1-52, 53-173, 174-307, or 573-591 of SEQ ID NO:103 and having kinase activity.

206. The kinase polypeptide molecule of claim 204 or claim 205 wherein said polypeptide is isolated, enriched or purified from a mammal.

207. The kinase polypeptide molecule of claim 206 wherein said mammal is a human.

208. An antibody or antibody fragment having specific binding affinity to a PAK5 kinase polypeptide having the complete amino acid sequence set forth in SEQ ID NO:103, a fragment thereof comprising at least 200 contiguous amino acids of SEQ ID NO:103 and having kinase activity or having the amino acid sequence set forth in SEQ ID NO:103 except that it lacks one or more of the domains defined by amino acid segments 1-52, 53-173, 174-307, or 573-591 of SEQ ID NO:103.

209. A hybridoma which produces an antibody having specific binding affinity to a PAK5 kinase polypeptide having the complete amino acid sequence set forth in SEQ ID NO:103, a fragment thereof comprising at least 200 contiguous amino acids of SEQ ID NO:103 and having kinase activity or having the amino acid sequence set forth in SEQ ID NO:103 except that it lacks one or more of the domains defined by amino acid segments 1-52, 53-173, 174-307, or 573-591 of SEQ ID NO:103.

210. A method for identifying a substance that modulates kinase activity comprising the steps of:

(a) contacting a PAK5 kinase polypeptide having the complete amino acid sequence set forth in SEQ ID NO:103, a fragment thereof comprising at least 200 contiguous amino acids of SEQ ID NO:103 and having kinase activity

or having the amino acid sequence set forth in SEQ ID NO:103 except that it lacks one or more of the domains defined by amino acid segments 1-52, 53-173, 174-307, or 573-591 of SEQ ID NO:103 with a test substance;

- (b) measuring the activity of said polypeptide; and
- (c) determining whether said substance modulates the activity of said polypeptide.

211. A method for identifying a substance that modulates kinase activity comprising the steps of:

- (a) expressing a PAK5 kinase polypeptide having the complete amino acid sequence set forth in SEQ ID NO:103, a fragment thereof comprising at least 200 contiguous amino acids of SEQ ID NO:103 and having kinase activity or having the amino acid sequence set forth in SEQ ID NO:103 except that it lacks one or more of the domains defined by amino acid segments 1-52, 53-173, 174-307, or 573-591 of SEQ ID NO:103;

- (b) adding a test substance to said cell; and
- (c) monitoring a change in cell phenotype or the interaction between said polypeptide and a natural binding partner.

212. A method for detection of a PAK5 kinase polypeptide in a sample as a diagnostic tool for a disease or disorder wherein said method comprises:

- (a) contacting said sample with a nucleic acid probe which specifically hybridizes, under hybridization conditions which are at least as stringent as hybridization in 50% formamide, 5X SSC, 50mM  $\text{NaH}_2\text{PO}_4$ , pH6.8, 0.5% SDS, 0.1 mg/ml sonicated salmon sperm DNA and 5X Denhart solution at 42°C; overnight washing with 2X SSC, 0.1% SDS at 45°C; and washing with 0.2X SSC, 0.1% SDS at 45°C to a PAK5 kinase nucleic acid target region that,

encodes the complete amino acid sequence as set forth in SEQ ID NO:103 or is the complement of all of the nucleotides thereof, encodes at least 200 contiguous amino acids of the amino acid sequence set forth in SEQ ID NO:103 and having kinase activity or the complement of all of the nucleotides thereof, or encodes a polypeptide having kinase activity comprising the amino acid sequence set forth in SEQ ID NO:103 except that it lacks one or more of the domains defined by amino acid segments 1-52, 53-173, 174-307, or 573-591 of SEQ ID NO:103 or is the complement of all of the nucleotides thereof; and

(b) detecting the presence of the probe:target region hybrid as an indication of said disease.

213. The method of claim 212 wherein said disease or disorder is selected from the group consisting of immune-related diseases and disorders, organ transplantation, myocardial infarction, cardiovascular disease, stroke, renal failure, oxidative stress-related neurodegenerative disorders and cancer.

214. A method for detection of a PAK5 kinase polypeptide in a sample as a diagnostic tool for a disease or disorder wherein said method comprises:

(a) comparing a nucleic acid target region encoding said PAK5 kinase polypeptide in a sample, said kinase polypeptide having an amino acid sequence as set forth in SEQ ID NO:103, at least 200 contiguous amino acids thereof and having kinase activity, or the amino acid sequence as set forth in SEQ ID NO:103 except that it lacks one or more of the domains defined by amino acid segments 1-52, 53-173, 174-307, or 573-591 of SEQ ID NO:103, with a control nucleic acid target region encoding said PAK5 kinase polypeptide; and

(b) detecting differences in sequence or amount between said target region and said control target region as an indication of said disease or disorder.

215. The method of claim 214 wherein said disease or disorder is selected from the group consisting of immune-related diseases and disorders, organ transplantation, myocardial infarction, cardiovascular disease, stroke, renal failure, oxidative stress-related neurodegenerative disorders and cancer.

216. A method for treating a disease or disorder by administering to a patient in need of such treatment a substance that modulates the activity of a PAK5 kinase having an amino acid sequence as set forth in SEQ ID NO:103, at least 25 contiguous amino acids thereof and having kinase activity, or the amino acid sequence as set forth in SEQ ID NO:103 except that it lacks one or more of the domains defined by amino acid segments 1-52, 53-173, 174-307, or 573-591 of SEQ ID NO:103.

217. The method of claim 216 wherein said disease or disorder is selected from the group consisting of immune-related diseases and disorders, organ transplantation, myocardial infarction, cardiovascular disease, stroke, renal failure, oxidative stress-related neurodegenerative disorders and cancer.

218. The method of claim 216 or claim 217 wherein said substance modulates kinase activity *in vitro*.

219. The method of claim 218, wherein said substance is a kinase inhibitor.



STE20_h	MAHLRGFANQHSRV	DPEELFTKLDR	IGKGSFGEV	YKGI	43
MST3_h	MAHSPVQSGLPGMQNLKAD	DPEELFTKLEK	IGKGSFGEV	FKGI	47
STLK2_h	MAHSPVAVQVPGMQNNIAD	DPEELFTKLEK	IGKGSFGEV	FKGI	47
STLK3_h	TAAAPAAPAAPAPAAQAVGWPICRDAYELQ	EVI	IGSGATAV	QAAALCKPRQ	57
STE20_h	EVVAIKIIDLEEADEIEDIQQEITVLSQCDSPYIT	YFGSYLKST	KLWIIMEY	100	
MST3_h	KVVAIKIIDLEEADEIEDIQQEITVLSQCDSPYVTK	YYGSYLKDT	KLWIIMEY	104	
STLK2_h	QVVAIKIIDLEEADEIEDIQQEITVLSQCDSPYVTK	YYGSYLKGS	KLWIIMEY	104	
STLK3_h	ERVAIKRINLEKQCQTSMDLELLKEIQAMSQCSPNVVTYYT	SFVVKDEL	WLVMLKLLSG	114	
STE20_h	GSALDLLKPGP	LEET	YIATILREILKGLDYLHSE	KIHRDIKAAANVLL	148
MST3_h	GSALDLLKPGP	LEET	YIATILREILKGLDYLHSE	KIHRDIKAAANVLL	152
STLK2_h	GSALDLLKPGP	FDEFQ	IATILREILKGLDYLHSE	KIHRDIKAAANVLL	152
STLK3_h	GSMLDI	IKYIVNRGEHKNGV	LEET	YIATILREILKGLDYLHSE	171
STLK4_h					41
STE20_h	SEQGDVVKLADFGV	A	GQLTDTQIKRNTFVGTPFWMAPEVIK	QSA	198
MST3_h	SEHGEVVKLADFGV	A	GQLTDTQIKRNTFVGTPFWMAPEVIK	QSA	202
STLK2_h	SEQGDVVKLADFGV	A	GQLTDTQIKRNTFVGTPFWMAPEVIK	QSA	202
STLK3_h	GEDGSVQIADFGV	SA	FLATGGDVTRNKV	RK	227
STLK4_h	GEDGSVQIADFGV	SA	FLATGGDVTRNKV	RK	97

Fig. 1A

**Fig. 1B**

STE20_h	RQ--PRSQCLSTLVRRPVFGELKEKHKQSGGSVGAL	ENAFSLAEESC	PGISDKLM	405		
MST3_h	IPKRPFSQCLSTIIISPLFAELKEKSAQCGGNLGSIEEL	RGAIYLAEEAC	PGISDTMV	411		
STLK2_h	-----CLSMIIITPAFAELKQDENNASRNQAI	EEELKSI	AVAAACPGITDKMV	400		
STLK3_h	DY--REASSCAVNLVRLRLNSRKELNDIRFEFTPGRDT	ADGV	SQLFSA	GLVDGHDV	468	
STLK4_h	-----ISLVRLRLNSKELNDIRFEFTPGRDTA	EGV	SQLIS	AGLV	GRDL	366
STE20_h	VHLLVERVQRFS	HNRNHLTSTR		426		
MST3_h	AQLVQRRLQRYSL	SGGTS	SH	431		
STLK2_h	KKLLIEKFQKCS	ADESP		416		
STLK3_h	VI	VAAANLQKIVDDPKALKTLTFK	LASGCDGSEIPDEVK	LIGFAQLSVS		
STLK4_h	VI	VAAANLQKIVEEPQSNR	SVTFK	LASGVEGSDIPDDGK	LIGFAQLSIS	

Fig. 1C

Ste20_h	MAHLRGFANQHSRV	-----DPEELFTKLDRIGKGSFGEVYKKGIDNHTK	43
T19A5.2_ce	MTTTSDELPRQADD	SMKWDRIYIQKLDPEVIFTKQERIGRGSFGEVYKKGIDNRTG	57
Pak_sp	-----	-----LLYRNFKVIGQGSADVYSARQVGTN	26
STLK5_h	-----	-----	0
Ste20_h	EVVAIKIIDLEEADEIED	IQQEITVL SQCDSPYITRYFGSYLKSTKLWIIIMEYLG	100
T19A5.2_ce	RVVAIKIIDLEQAEDIED	IQQEIQVLSQCDSQYVTKYFGSFLKGSKLWIIIMEYLG	114
Pak_sp	LSVAIKIMNINQQPKKEF	-IVNEILVMKSHHKNIVNFIDTFFYKSELWMVMEYMRG	82
STLK5_h	-----	-----	0
Ste20_h	GSA LDL LKPGPL	LEET YIA TILREIL KGLDYLH SERKIH RD IKAANVL	157
T19A5.2_ce	GSA LDL TKSGL	LDESHIAVILREIL KGLEYLH SERKIH RD IKAANVL	171
Pak_sp	GSLTEVVTNNTL	SEGGQIAAICKEITLEGLQLHENGIVHRDIKSDN	139
STLK5_h	--LICTHFMDGMNELA	IAYILIQGVLKALDYIHHMGYVHRISVKASHILISVDGKVYLS	55
Ste20_h	DFGVAGQLTDTQIKRNT	TFVGTPTFWMAPEVIKQSA--YDFKAD IWSL GITA	205
T19A5.2_ce	DFGVAGQLTETVKRRI	TFVGSPTFWMAPELIKQSS--YDIYKAD IWSL GITA	219
Pak_sp	DFGFCAGQIDSNMTKR	TTIMVGTPTFWMAPEVVTTRKE--YGFKVVDVWSL GIMA	187
STLK5_h	GLRSNLSMISAGQRQR	VVHDFPKYSVKVLPWLSPEVILQQLN LQG YDAKSDIYSV GITA	112
Ste20_h	IELAKGEPN	SDLHPMRVLF LI PK-NSPPTLEG-Q	238
T19A5.2_ce	IELANGEPH	SDLHPMRVLF LI PK-NPPVLLQGSQ	253
Pak_sp	IEMVEGEP	PYLNNP LRALYLIATIGTPKISRPEL	222
STLK5_h	CELANGHVP	FKDMPATQMLLEKLN-GTVPCLLD-TSTIPAEELTMSPSRVANSGLS	167

Fig. 2A

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**Fig. 2B**

ZC504.4_ce	MSSSGEDE---	IDLNSLRDPAGIFEL	IEVVGNGTYGQVYK	GRHVKTALQ	LAAAIKIMNINE	58	
NIK_m	MANDSPAKSLVD	IDLSSLRDPAGIFEL	VEVVGNGTYGQVYK	GRHVKTIVT	-AAIKVMDVTE	69	
ZC1_h	MANDSPAKSLVD	IDLSSLRDPAGIFEL	VEVVGNGTYGQVYK	GRHVKTIVT	-AAIKVMDVTE	60	
ZC2_h	-----	-----	-----	-----	-----	28	
ZC3_h	-----	-----	-----	-----	-----	28	
ZC504.4_ce	DEEIDEIKLEINMLKKH	SHHRNVATYYGAFIKK	LLPSSSTGKH	DDLWLVMFEFCG	SGSITDLVK	116	
NIK_m	DEEEETLEINMLKKY	SHHRNIATYYGAFIKK	SPPGHD	--DDLWLVMFEFCG	SGSITDLVK	117	
ZC1_h	DEEEETLEINMLKKY	SHHRNIATYYGAFIKK	SPPGHD	--DDLWLVMFEFCG	SGSITDLVK	118	
ZC2_h	DEEEETLEINMLKKY	SHHRNIATYYGAFIKK	SPPGMD	--DDLWLVMFEFCG	SGSITDLIK	84	
ZC3_h	DEEEETLEINMLKKY	SHHRNIATYYGAFIKK	SPPGND	--DDLWLVMFEFCG	SGSITDLVK	84	
ZC504.4_ce	NTKGGSLKEE	WIAIYICREILRGLY	HLHQS	KVIHRDIKQNVLLT	DSAEVKLVDFGVSAQL	176	
NIK_m	NTKGNLTKEDWIAIYI	SREILRGLAHLHI	HHHVIHRDIKQNVLLT	TENAEVKLVDFGVSAQL		177	
ZC1_h	NTKGNLTKEDWIAIYI	SREILRGLAHLHI	HHHVIHRDIKQNVLLT	TENAEVKLVDFGVSAQL		178	
ZC2_h	NTKGNLTKEDWIAIYI	SREILRGLAHLHI	HHHVIHRDIKQNVLLT	TENAEVKLVDFGVSAQL		144	
ZC3_h	NTKGNLTKEDWIAIYI	SREILRGLAHLHI	HHHVIHRDIKQNVLLT	TENAEVKLVDFGVSAQL		144	
ZC504.4_ce	DKTVGRRNTFIGTPY	WMAPEVIACDES	PEIATYDS	RSDDLWSL	GITALEMAEGH	PPLCDMHP	236
NIK_m	DRTVGRRNTFIGTPY	WMAPEVIACDEN	PDATYD	YRSDDLWS	CGITALEMAEG	PPLCDMHP	237
ZC1_h	DRTVGRRNTFIGTPY	WMAPEVIACDEN	PDATYD	YRSDDLWS	CGITALEMAEG	PPLCDMHP	238
ZC2_h	DRTVGRRNTFIGTPY	WMAPEVIACDEN	PDATYD	YRSDDLWS	CGITALEMAEG	PPLCDMHP	204
ZC3_h	DRTVGRRNTFIGTPY	WMAPEVIACDEN	PDATYD	YRSDDLWS	CGITALEMAEG	PPLCDMHP	204

Fig. 3A

ZC504_4_ce	RHSPASRPRPRSPQIQSHPAAPHLADLANYEKRRRSEREEERREREQAHHAMPIARVSA SV	473
NIK_m	EQKEQRRRLLEEQQRRREAREARRQEQEREQRRREQEKKRRLEELERRRKKEEEEERRRAEEEEKR	458
ZC1_h	EQKEQRRRLLEEQQRRREAREARRQEQEREQRRREQEKKRRLEELERRRKKEEEEERRRAEEEEKR	459
ZC2_h	EEQKEQRRRLLEEQQRRREKELRKQKQEREQRRIHYEEQMRR-----EEEEER	404
ZC3_h	EEQKFERRRVVEEQRRREEQRKLQEKEQQRRLLEDMA L-----RREEEER	409

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**Fig. 3C**



ZC504.4\_ce -----NSGHGAYKGGKIPERPGIISL-DDDDSD 623  
 NIK\_m -----AWSRSDSEVPVPRVVRTTSRSPVLSRRDSPILQGGGQNS 639  
 ZC1\_h -----PQVPVRTTSRSPVLSRRDSPILQ-GSGQQN 648  
 ZC2\_h NSDPTSENPLPTRIEKFDRSSWLREQEEDIPPKVPQRTTISIPALARKNSP GNGSALGPR 635  
 ZC3\_h NSDPTSEGGPSNPP-----AWVRPD-NEAPPKVPQRTTISIPALNTSGAGGSRPAQAVR 689  
  
 ZC504.4\_ce SDNE-----EGNEPLMFKPIVRCPFISFFWFLS-- 651  
 NIK\_m QAGQ-----RNSTSSIEPRLLWERVEKLVPRPG-- 667  
 ZC1\_h SQAG-----QRNSTSIEPRLLWERVEKLVPRPG-- 676  
 ZC2\_h LGSQ-----PIRASNPDLRRTETPILESPLQRTSSG 665  
 ZC3\_h ARPRNSAWQIYLQRRRAERGTPKPPGPAQPPGPNASSNPDLRSDPG-----WERS-- 742  
  
 ZC504.4\_ce --ANVIHSVDGSIPLVKHLIWFQNASSSRIGALPDLLPKSPCLRRQINDQTRQMSDDRADE 709  
 NIK\_m --SSSSSSNSGSGSQSGSGSGERFVRSSSSKSESGSPSPRQESAKKPPDKKEVF 725  
 ZC1\_h --SSSSSSNSGSGSQSGSGSGERFVRSSSSKSESGSPSPRQESAKKPPDKKEVF 734  
 ZC2\_h SSSSSSTPSSSQSSQSGSQSGSQSSERTRVRANSSKSESGSPVLPHEPAKVKEESRDIT 725  
 ZC3\_h --DSVLPASHGHP-----QAGSLERNRVGVSSSKPDSSPVLSPGNKA[K]PDDHRSRPG 792  
  
 ZC504.4\_ce QPNGFQ-----NSDSR-----SSIQHSFSNRDREKISFVGIFGGGAGAGGGTIVNRPG-- 755  
 NIK\_m RSLKPA[PA]GEV-----DLTAL-----AKELRAVEIDVRPPHKVTDYSSSSEESGTTDEEEEDVED 777  
 ZC1\_h RPLKPA-----DLTAL-----AKELRAVEIDVRPPHKVTDYSSSSEESGTTDEEDDVEEQ 783  
 ZC2\_h RPSRPA[PA]SYKKAIDEDLTALAKELRELRIEETNRPMKKVTDYSSSSEESSESSEEEEDGES 785  
 ZC3\_h RPADFV-----L-----LKERTLDEAPRPPKKAMDYSSSSEEVESSEDDDEEGEG 837

Fig. 3D

Fig. 3E

ZC504.4_ce	DQM	T	V	L	E	G	Q	N	I	L	A	T	I	S	G	R	K	R	R	I	R	V	Y	L	S	W	L	R	Q	K	I	L	R	T	E	G	A	G	S	A	N	T	T	E	K	R	N	G	W	V	N	V	G	D	--	889					
NIK_m	QQM	D	V	L	E	G	L	N	V	L	T	I	S	G	K	K	D	K	L	R	V	Y	L	S	W	L	R	N	K	I	L	H	N	D	P	E	V	--	--	E	K	K	Q	G	W	T	T	V	G	D	--	1013									
ZC1_h	QQM	D	V	L	E	G	L	N	V	L	T	I	S	G	K	K	D	K	L	R	V	Y	L	S	W	L	R	N	K	I	L	H	N	D	P	E	V	--	--	E	K	K	Q	G	W	T	T	V	G	D	--	1019									
ZC2_h	QQM	D	V	L	E	G	L	N	V	L	T	I	S	G	K	K	N	K	L	R	V	Y	L	S	W	L	R	N	R	I	L	H	N	D	P	E	V	--	--	E	K	K	Q	G	W	I	T	V	G	D	--	1077									
ZC3_h	QQM	D	V	L	E	G	L	N	L	I	T	I	S	G	K	R	N	K	L	R	V	Y	L	S	W	L	R	N	K	I	L	H	N	D	P	E	V	--	--	E	K	K	Q	G	W	I	T	V	G	D	--	1106									
ZC4_h	RQL	Q	V	L	E	P	L	N	L	I	T	I	S	G	H	K	N	R	L	R	V	Y	H	L	T	W	L	R	N	K	I	L	N	D	P	E	S	--	--	K	R	R	Q	E	E	M	L	K	T	E	E	A	C	120							
ZC504.4_ce	--	--	--	--	L	Q	G	A	I	H	F	K	I	V	R	Y	E	R	I	K	F	L	V	V	G	L	E	S	S	I	E	I	Y	A	W	A	P	K	P	Y	H	K	F	M	S	F	K	S	F	G	S	L	S	H	V	P	L	I	V	944	
NIK_m	--	--	--	--	L	E	G	C	V	H	Y	K	V	V	K	Y	E	R	I	K	F	L	V	I	A	L	K	S	S	V	E	V	Y	A	W	A	P	K	P	Y	H	K	F	M	A	F	K	S	F	G	E	L	L	H	K	P	L	L	V	1068	
ZC1_h	--	--	--	--	L	E	G	C	V	H	Y	K	V	V	K	Y	E	R	I	K	F	L	V	I	A	L	K	S	S	V	E	V	Y	A	W	A	P	K	P	Y	H	K	F	M	A	F	K	S	F	G	E	L	V	H	K	P	L	L	V	1074	
ZC2_h	--	--	--	--	L	E	G	C	I	H	Y	K	V	V	K	Y	E	R	I	K	F	L	V	I	A	L	K	N	A	V	E	I	Y	A	W	A	P	K	P	Y	H	K	F	M	A	F	K	S	F	A	D	L	Q	H	K	P	L	L	V	1132	
ZC3_h	--	--	--	--	M	E	G	C	H	Y	R	V	V	K	Y	E	R	I	K	F	L	V	I	A	L	K	S	S	V	E	V	Y	A	W	A	P	K	P	Y	H	K	F	M	A	F	K	S	F	A	D	L	P	H	R	P	L	L	V	1161		
ZC4_h	K	A	I	D	K	L	T	G	C	E	H	F	S	V	L	Q	H	E	T	T	Y	I	A	I	A	L	K	S	S	I	H	L	Y	A	W	A	P	K	S	F	D	E	S	T	A	I	K	V	E	P	T	L	D	H	K	P	V	T	V	180	
ZC504.4_ce	D	L	T	V	E	D	N	A	R	L	K	V	L	Y	G	S	T	G	F	H	A	I	D	L	D	S	A	A	V	D	I	Y	T	P	A	Q	S	G	Q	T	T	I	P	H	C	I	V	V	L	P	N	S	N	G	M	Q	L	L	1004		
NIK_m	D	L	T	V	E	E	G	Q	R	L	K	V	I	Y	G	S	C	A	G	F	H	A	V	D	V	D	S	G	S	V	Y	D	I	Y	L	P	T	H	I	Q	C	S	I	K	P	H	A	I	I	L	P	N	T	D	G	M	E	L	L	1128	
ZC1_h	D	L	T	V	E	E	G	Q	R	L	K	V	I	Y	G	S	C	A	G	F	H	A	V	D	V	D	S	G	S	V	Y	D	I	Y	L	P	T	H	I	Q	C	S	I	K	P	H	A	I	I	L	P	N	T	D	G	M	E	L	L	1134	
ZC2_h	D	L	T	V	E	E	G	Q	R	L	K	V	I	F	G	S	H	T	G	F	H	V	I	D	V	D	S	G	N	S	Y	D	I	Y	T	P	S	H	I	Q	G	N	I	T	P	H	A	I	V	I	L	P	K	T	D	G	M	E	M	L	1192
ZC3_h	D	L	T	V	E	E	G	Q	R	L	K	V	I	Y	G	S	S	A	G	F	H	A	V	D	V	D	S	G	N	S	Y	D	I	Y	I	P	V	H	I	Q	S	I	T	P	H	A	I	I	F	L	P	N	T	D	G	M	E	M	L	1221	
ZC4_h	D	L	A	I	G	S	E	K	R	L	K	I	F	F	S	S	A	D	G	Y	H	L	I	D	A	E	S	E	V	M	S	D	V	T	L	P	K	N	P	L	E	I	I	P	Q	N	I	I	L	P	D	C	L	G	I	G	M	M	240		

Fig. 3F

ZC504.4_ce	L	C	Y	D	N	E	G	V	V	N	T	Y	G	R	M	T	K	N	V	V	L	Q	W	E	M	P	S	V	A	Y	I	S	T	G	Q	I	M	G	W	G	N	K	A	I	E	I	R	S	V	D	T	G	H	L	D	G	V	1064		
NIK_m	V	C	Y	E	D	E	G	V	V	N	T	Y	G	R	I	T	K	D	V	V	L	Q	W	E	M	P	T	S	V	A	Y	I	R	S	N	Q	T	I	M	G	W	G	E	K	A	I	E	I	R	S	V	E	T	G	H	L	D	G	V	1188
ZC1_h	V	C	Y	E	D	E	G	V	V	N	T	Y	G	R	I	T	K	D	V	V	L	Q	W	E	M	P	T	S	V	A	Y	I	R	S	N	Q	T	I	M	G	W	G	E	K	A	I	E	I	R	S	V	E	T	G	H	L	D	G	V	1194
ZC2_h	V	C	Y	E	D	E	G	V	V	N	T	Y	G	R	I	T	K	D	V	V	L	Q	W	E	M	P	T	S	V	A	Y	I	H	S	N	Q	I	M	G	W	G	E	K	A	I	E	I	R	S	V	E	T	G	H	L	D	G	V	1252	
ZC3_h	L	C	Y	E	D	E	G	V	V	N	T	Y	G	R	I	T	K	D	V	V	L	Q	W	E	M	P	T	S	V	A	Y	I	C	S	N	Q	I	M	G	W	G	E	K	A	I	E	I	R	S	V	E	T	G	H	L	D	G	V	1281	
ZC4_h	L	T	F	N	A	E	A	L	S	V	E	A	N	E	Q	L	F	K	K	I	L	E	M	W	K	D	I	P	S	I	A	F	E	C	T	D	R	T	T	G	W	Q	K	A	I	E	V	R	S	L	Q	S	R	V	L	E	S	E	300	
ZC504.4_ce	F	M	H	K	K	A	Q	K	L	K	F	L	C	E	R	N	D	K	V	F	F	S	S	A	K	G	G	S	C	Q	I	Y	F	M	T	L	N	K	P	G	L	T	N	W	1109															
NIK_m	F	M	H	K	R	A	Q	R	L	K	F	L	C	G	R	N	D	K	V	F	F	S	S	V	R	S	G	G	S	Q	V	Y	F	M	T	L	G	R	T	S	L	S	W	1233																
ZC1_h	F	M	H	K	R	A	Q	R	L	K	F	L	C	E	R	N	D	K	V	F	F	S	S	V	R	S	G	G	S	Q	V	Y	F	M	T	L	G	R	T	S	L	S	W	1239																
ZC2_h	F	M	H	K	R	A	Q	R	L	K	F	L	C	E	R	N	D	K	V	F	F	S	S	V	R	S	G	G	S	Q	V	F	F	M	T	L	N	R	N	S	M	M	N	W	1297															
ZC3_h	F	M	H	K	R	A	Q	R	L	K	F	L	C	E	R	N	D	K	V	F	F	S	S	V	R	S	G	G	S	Q	V	Y	F	M	T	L	N	R	N	R	I	M	N	W	1326															
ZC4_h	L	K	R	R	S	I	K	L	R	F	L	C	T	R	G	D	K	L	F	E	T	S	T	L	R	N	H	S	R	V	Y	F	M	T	L	G	K	L	E	E	L	Q	S	N	Y	D	V	349												

Fig. 3G

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**Fig. 4A**

```

KHS1_h 362 -----SDPNFMLQWNP-----FV-----D 375
KHS2_h 359 LDSSEEIYYTARSNLDLQLEYGQGQGYFLGANKSLKSVEEELHQRGHVAHLEDDEGD 418

      ** * ***** * .. * .. * .. * .. * .. * .. *
      . . GANTGKSTSKRAIPPLPPKPRISSYPED-NFPDEEKASTIKHCP--DSESRAPQILRRQ 432
KHS1_h 376
KHS2_h 419 DDESKHSTLKAKIPPLPPKPKSIFIPQEMHSTEDENQGTIKRCPMMSGSPAKPSQVPPRP 478

      * .. * .. * .. * .. * .. * .. * .. * .. *
      . . SSPSCGPVAETSSIGNGDGISKL-MSENTEGSA-----QAPQLPRKNDKRDFFKPAIN 484
KHS1_h 433
KHS2_h 479 PPPR--LPPHKPVALGNMGSSFFQLMGERDGSQCQQQNEHRGTNLSRK-EKKDVPKPISN 534

      ***** ***** ***** ***** ***** ***** *****
      ***** GLPPTPKVLMGACFSKVFDDGCPLKINCATSWIHPDTKDQYIIFGTEDGIYTLNLNELHEA 544
KHS1_h 485
KHS2_h 535 GLPPTPKVHMGACFSKVFNGCPLKIHCASSWINPDTRDQYLIFGAEEGIYTLNLNELHET 594

      ***** ***** ***** ***** ***** ***** *****
      ***** TMEQLFPRKCTWLYYVINNTLMSLSEKTFQLYSHNLIALFEHAK-KPGLAAHIQTHRFPD 603
KHS1_h 545
KHS2_h 595 SMEQLFPRRCTWLYYVMNNCLLSIS-GKASQLYSHNLPGLFDYARQMQLPVAIPAHKLDP 653

      ***** ***** ***** ***** ***** ***** *****
      ***** RILPRKFALTTKIPDTKGCHKCCIVRNPTYTGHKYLCCGALQSGIVLLQWYEPMQKFMLIKH 663
KHS1_h 604
KHS2_h 654 RILPRKFSVSAKIPETKWCQKCCVVRNPTYTGHKYLCCGALQTSIVLLEWVEPMQKFMLIKH 713

```

Fig. 4B

```

**.* **.* **.* **.* **.* **.* **.* **.* **.* **.* **.* **.* **.* **.* **.* **.* **.* **.* **.* **.*
KHS1_h 664 FDFPLPSPLNVFEMLVIPPEQEYPMVCVAISKGTESNQVVQFETINLNSASSWFTEIGAGS 723
KHS2_h 714 IDFPICPLRMFEMLVVPEQEYPLVCVGVSRGRDFNQVVRFFETVNPNSTSSWFTE--SDT 771

*.* **.* **.* **.* **.* **.* **.* **.* **.* **.* **.* **.* **.* **.* **.* **.* **.* **.* **.* **.*
KHS1_h 724 QQLDSIHVTQLERDTVLVCLDKFVKIVNLQGKLSKSKKLASELSFDFRIESVVCCLQDSVL 783
KHS2_h 772 PQTNVTHVTQLERDTILVCLDCCIKIVNLQGRLKSSRKLSSSELTDFQIESIVCLQDSVL 831

**.* **.* **.* **.* **.* **.* **.* **.* **.* **.* **.* **.* **.* **.* **.* **.* **.* **.* **.* **.*
KHS1_h 784 AFWKHGMQGKSFKSDEVTQEISDETRVFRLLGSDRVVVLSESRPTENPTAHSNLYILAGHE 843
KHS2_h 832 AFWKHGNQGRSFRSNEVTQEISDSTRIFRLLGSDRVVVLSESRPTDNPTANSNLYILAGHE 891

**.*
KHS1_h 844 NSY 846
KHS2_h 892 NSY 894

```

Fig. 4C

SULU\_ce MAPAVLQKPGVIAKDPSTIAALFSNKKDPEQRYQDLREIGHGSFGAVYFAYDKKNEQTVAIKK 60  
 SULU1\_h - - - - MRKGV LKDP EIDDLFFYKDDPEELFIGLHHEIGHGSFGAVYFATNAHTNEVVAIKK 54  
 SULU3\_m - - MPSTNRAGSLKDP EIAELFFFKEDPEKLF TDLREIGHGSFGAVYFARDVRTNEVVAIKK 58

SULU\_ce M N F S G K Q A V E K W N D I L K E V S F L N T V V H P H I V D Y K A C F L K D T T C W L V M E Y C I G S A A D I V D V 120  
 SULU1\_h M S Y S G K Q T H E K W Q D I L K E V K F L R Q L K H P N T I E Y K G C Y L K E H T T A W L V M E Y C I G S A S D L L E V 114  
 SULU3\_m M S Y S G K Q S T E K W Q D I I K E V K F L L Q R I K H P N S I E Y K G C Y L R E H T T A W L V M E Y C I G S A S D L L E V 118

SULU\_ce L R K G M R E V E I A A I C S Q T L D A L R Y L H S L K R I H R D I K A G N I L L S D H A I V K L A D F G S A S L V D P 180  
 SULU1\_h H K K P L Q E V E I A A I T H G A L H G L A Y L H S H A L I H R D I K A G N I L L T E P G Q V K L A D F G S A S M A S P 174  
 SULU3\_m H K K P L Q E V E I A A I T H G A L Q G L A Y L H S H T M I H R D I K A G N I L L T E P G Q V K L A D F G S A S M A S P 178

SULU\_ce A Q T F I G T P F F M A P E V I L A M D E G H Y T D R A D I W S L G I T C I E L A E R R P P L F S M N A M S A L Y H I A 240  
 SULU1\_h A N S F V G T P Y W M A P E V I L A M D E G Q Y D G K V D I W S L G I T C I E L A E R K P P L F N M N A M S A L Y H I A 234  
 SULU3\_m A N S F V G T P Y W M A P E V I L A M D E G Q Y D G K V D I W S L G I T C I E L A E R K P P L F N M N A M S A L Y H I A 238  
 SULU3\_h - - - - - - - - - - - - - - - - I T E L A E R K P P L F N M N A M S A L Y H I A 24

SULU\_ce Q N D P P T L S P I D T S E Q P E W S L E F V Q F I D K C L R K K P A E E R M S A E E C F R H P F I Q R S R P S D T I Q E 300  
 SULU1\_h Q N D S P T L Q S N - - - - - E W T D S E R R F V D Y C L Q K I P Q E R P T S A E L L R H D F V R R D R P L R V L I D 288  
 SULU3\_m Q N E S P T L Q S N M N - - - - - D S C L Q K I P Q D R P T S E E L L K H M F V L R E R P E T V L I D 284  
 SULU3\_h Q N E S P T L Q S N - - - - - E W S D Y F R N F V D S C L Q K I P Q D R P T S E E L L K H I F V L R E R P E T V L I D 78

SULU\_ce L I Q R T K N M V L E L D N F Q Y K K M R K L M Y L D E T E G K E G S E G N G A S D D L D F H G N E A N S I G R A G D S 360  
 SULU1\_h L I Q R T K D A V R E L D N L Q Y R K M K K I L F - 313  
 SULU3\_m L I Q R T K D A V R E L D N L Q Y R K M K K L L F - 309  
 SULU3\_h L I Q R T K D A V R E L D N L Q Y R K M K K L L F - 103

Fig. 5A



SULU_ce	S	K	E	E	K	M	R	V	R	C	S	Q	N	N	E	L	D	K	R	K	K	D	I	E	D	G	E	K	K	M	K	K	T	K	N	S	Q	N	Q	Q	M	K	L	Y	S	A	Q	Q	L	K	E	Y	K	Y	N	K	E	A	Q	K	I	641
SULU1_h	S	I	E	L	E	K	L	A	K	K	Q	V	A	I	I	E	K	E	A	K	V	A	A	A	D	E	K	F	Q	Q	I	L	A	Q	Q	K	K	D	L	T	T	F	L	E	S	Q	K	K	Q	Y	K	I	C	K	E	K	I	K	I	564		
SULU3_m	A	A	E	M	E	K	L	I	K	K	H	Q	A	A	M	E	K	E	A	K	V	M	A	N	E	E	K	F	Q	Q	H	I	Q	A	Q	Q	K	E	L	N	S	F	L	E	S	Q	K	R	E	Y	K	L	R	K	E	Q	L	K	I	559		
SULU3_h	A	A	E	M	E	K	L	I	K	K	H	Q	A	A	M	E	K	E	A	K	V	M	S	N	E	E	K	F	Q	Q	H	I	Q	A	Q	Q	K	E	L	N	S	F	L	E	S	Q	K	R	E	Y	K	L	R	K	E	Q	L	K	I	353		

**Fig. 5B**

SULU_ce	E	L	E	E	L	I	A	Y	Q	K	T	R	A	T	L	E	E	Q	I	K	K	E	R	T	A	L	E	E	R	I	G	T	R	R	A	M	L	E	Q	K	I	I	E	E	R	E	Q	M	G	E	M	R	R	L	K	K	E	Q	I	940			
SULU1_h	E	M	E	L	L	N	A	Y	Q	S	K	I	K	M	Q	T	E	A	Q	H	E	R	E	L	Q	K	L	E	L	E	Q	R	V	S	L	R	R	A	H	L	E	Q	K	I	E	E	L	A	A	L	Q	K	E	R	S	E	R	I	K	N	L	864	
SULU3_h	E	L	E	L	L	N	A	Y	Q	S	K	I	K	M	Q	A	L	E	A	Q	H	D	R	E	L	R	E	L	L	E	Q	R	V	S	L	R	R	A	L	L	E	Q	K	I	E	E	E	M	L	A	L	Q	N	E	R	T	E	R	I	R	S	L	653

**Fig. 5C**

SULU\_ce RD[R]HSQ[E]RHRLENHFVR[T]G[STSRSSGGIAPGVGNSSSIQMAM 982  
 SULU1\_h LE[R]QER[E]ETFDMESLR[M]G[F]GNLVTLDFFPKEDYR 898  
 SULU3\_h LE[R]QAR[E]IEAFDSESMR[L]G[F]SNMVLNLSPEAFSHSYPGASGWSHNPTGGPGPHWGHPMG 713  
 SULU3\_h GPPQAWGHPMQGGPQPWGHPSGPMQGVPRGSSMGVRNSPQALRRRTASGGRTEQGMSRSTS 773  
 SULU3\_h VTSQISNGSHMSYT 787

# Fig. 5D

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* * * * * . . . . . * * * * * . . . . . * * * * * . . . . . * * * * *
361 S-STPLPPSQPEPVNGPCSPQSGDGPLQTTSPADGLSKNDNDLKVVPVPLKRSRPLSMDA 419
GEK2_h 361 SPSTPLAPSQSQDSVNEPCSPQSGDRSLQTTSPVAVPGNENGLAVPVPLKRSRPPVSMMDA 420

* * * * * . . . . . * * * * * . . . . . * * * * * . . . . . * * * * *
420 RIQMDEEKQIPDQDENPSPAASKSQKANQSRPNSSALETLGGEALTNGGLELPSSVTPSH 479
GEK2_h 421 RIQVAQEKQVAEQGGDLSPAANRSQKASQSRPNSSALETLGGEKLANGSLEPPAQAAAGP 480

* * * * * . . . . . * * * * * . . . . . * * * * * . . . . . * * * * *
480 SKRASDCSNLSTSESMGYGTSLSADLSLNKETGSLSLKGSKLNKTKLKRTRRFVVDGVEV 539
GEK2_h 481 SKRSDCCSSLCTSESMGYGTNLSTDLSLNKEMGSLSIKDPKLYKKTTLKRTRKFVVDGVEV 540

* * * * * . . . . . * * * * * . . . . . * * * * * . . . . . * * * * *
540 SITTSKIISEDEKKDEEMRFLRRQELRELRLQLKEEHRNQTQLSSKHQLQEQMHKRFEQ 599
GEK2_h 541 SITTSKIISEDEKKDEEMRFLRRQELRELRLQLKEEHRNQTQLSNKHQLQEQMHKRFEQ 600

* * * * * . . . . . * * * * * . . . . . * * * * * . . . . . * * * * *
600 EINAKKKFYDVELENLERQKQKQVEKMEQDHSVRRKKEEAKRIRLEQDRDYAKFQEQLKQM 659
GEK2_h 601 EINAKKKFFDTELENLERQKQKQVEKMEQDHAVRRRREEARRIRLEQDRDYTRFQEQLKLM 660

* * * * * . . . . . * * * * * . . . . . * * * * * . . . . . * * * * *
660 KKEVKSEVEKLPRQQRKESMKQMEEHSQKKQLDRDRDFVAKQKEDLELAMRKLTTENRRE 719
GEK2_h 661 KKEVKNEVEKLPRQQRKESMKQMEEHTQKKQLDRDRDFVAKQKEDLELAMRKLTTDNRR 720

```

Fig. 6B

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**Fig. 6C**

**SUBSTITUTE SHEET (RULE 26)**

**Fig. 7A**

	PAK1_h	PAK65_h	PAK3_m	PAK4_h	PAK5_h
1	GQ	GQ	GQ	GQ	GQ
2	GA	GA	GA	GA	GA
3	SG	SG	SG	SG	SG
4	TV	TV	TV	TV	TV
5	YT	YT	YT	YT	YT
6	AM	AM	AM	AM	AM
7	DV	DV	DV	DV	DV
8	IA	IA	IA	IA	IA
9	TT	TT	TT	TT	TT
10	GE	GE	GE	GE	GE
11	QA	QA	QA	QA	QA
12	IK	IK	IK	IK	IK
13	QM	QM	QM	QM	QM
14	NL	NL	NL	NL	NL
15	QQ	QQ	QQ	QQ	QQ
16	PK	PK	PK	PK	PK
17	KE	KE	KE	KE	KE
18	LI	LI	LI	LI	LI
19	NE	NE	NE	NE	NE
20	IL	IL	IL	IL	IL
21	VM	VM	VM	VM	VM
22	MR	MR	MR	MR	MR
23	EN	EN	EN	EN	EN
24	KN	KN	KN	KN	KN
25	PN	PN	PN	PN	PN
26	IV	IV	IV	IV	IV
27	NY	NY	NY	NY	NY
28	LD	LD	LD	LD	LD
29	SY	SY	SY	SY	SY
30	LV	LV	LV	LV	LV
31	336	297	334	473	194

**SUBSTITUTE SHEET (RULE 26)**



**SUBSTITUTE SHEET (RULE 26)**

**Fig. 7C**

SEQ ID NO: 5 STLK2 human Nterm=1-21 kin=22-274

Cterm=275-416

MAHSPVAVQVPGMQNNIADPEELFTKLERIGKGSFGEVFKGIDNRTQQVVAIKIIDLEEA  
EDEIEDIQQEITVLSQCDSSYVTKYYGSYLKGSKLWIIMEYLGGSALDLLRAGPFDEFQ  
IATMLKEILKGLDYHSEKKIHRDIKAANVLLSEQGDVKLADFGVAGQLTDTQIKRNTFV  
GTPFWMAPEVIQQSAYDSKADIWSLGITAIELAKGEPNSDMHPMRVFLIPKNNPPTLV  
GDFTKSFKEFIDACLNKDPSPFRPTAKELLKHKFIVKNSKTSYLTTELIDRFKRWKAEGHS  
DDES DSEGS DSESTSRENTHPEWSFTTVRKKPDPKKVQNGAEQDLVQTLSCLSMIITPA  
FAELKQQDENNASRNQAIEELEKSI AVAEAACPGITDKMVKKLIEKFQKCSADESP

SEQ ID NO: 6 STLK3 human Nterm=1-31 kin=32-308 Cterm=309-489

(insert=327-352) tail=490-516

TAAPAPAAPAAPAPAPAPAPAAQAVGWPICRDAYELQEVI GSGATAVVQAALCKPRQERV  
AIKRINLEKCQTSMDLLKEIQAMSQC SHPNVVTYYTSFVVKDELWLV MKLLSGGSMLDI  
IKYIVNRGEHKNGVLEEAIATILKEVLEGLDYLRNGQIHRDLKAGNILLGEDG SVQIA  
DFGVSAFLATGGDVTRNKVRKTFVGT PCWMAPEVMEQVRGYDFKADMWSFGITAIELATG  
AAPYHKYPPMKVLM LTLQNDPPTLETGVEDKEMMKY GKSFRKLLSLCLQKDPSKRPTAA  
ELLKCKFFQKAKNREYLIEKLLTRTPDIAQRAKKVRRVPGSSGHLHKTEDGDWEWSDDM  
DEKSEEGKAAFSQEKSRRVKEENPEIAVSASTIPEQIQSLSVHDSQGPPNANEDYREASS  
CAVNLVLR LRNSRKELNDIRFEFTPGRDTADGV SQELFSAGLV DGHVIVAANLQKIVD  
DPKALKTLTFKLASGCDGSEIPDEVKLIGFAQLSVS

SEQ ID NO: 7 STLK4 human Nterm=absent, kin=1-178, Ctail=179-414,  
insert1=198-222, insert2=253-293

KSGVLDXSTIATILREVLEGL EYLHKXGQIHRDV KAGNILXGEDG SVQIADFGVSAFLAT  
GGDITRNKVRKTFVGT PCWMAPEVMEQVRGYDFKADIWSFGITAIELATGAAPYHKYPPM  
KVLM LTLQNDPPSLETGVQDK EMLKKY GKSFRKMISLCLQKDPEKRPTAAELLRHKFFQK  
AKNKEFLQEKT LQRAPTISERAKK VRRVPGSSGRLHKTEDGGWEWSDDDEFDEESEEKAA  
ISQLRSPRVKESISNSELFPTTDPVGTLLQVPEQISAHLPQAPAGQIATQPTQVSLPPTAE  
PAKTAQALSSGSGSQETKIPISLVLR LRNSKKE LNDIRFEFTPGRDTAEGV SQELISAGL  
VDGRDLVIVAANLQKIVEEPQSNRSVTFKLASGVEGSDIPDDGKLIGFAQLSIS

SEQ ID NO: 8 STLK5 human Nterm=absent, kin=1-222(lacks N-term),  
Ctail=224-274

LICTHFMDGMNELAIAYILQGV LKALDYIHHMGYVHRSVKASHILISVDGKVYLSGLRSN  
LSMISHGQRQRVVHDFPKYSVKVLPWLSPEVLQQN LQGYDAKSDIYSVGITACELANGHV  
PFKDMPATQMLLEKLN GTVPCLLD TSTIPAEELTMSPSRSVANSGLSDSLTTSTPRPSNG  
DSPSHPYHRTFSPHFHHFVEQCLQRNP DARPSASTLLNHSFFKQIKRRASEALPELLRPV

**Fig. 8A**

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TPITNFEQSQSDHSGIFGLVTNLEELEVDDWEF

SEQ ID NO: 13 ZC1 human 1/5/98 Nterm=1-22 kin=23-289

coiled-coil=290-526 pro=527-640 B=641-896 Rab/Rac-BD=897-1239

MANDSPAKSLVDIDLSSLRDPAGIFELVEVVGNGTYGQVYKGRHVKTGQLAAIKVMDVTE  
DEEEEIKLEINMLKKYSHRNIATYYGAFIKKSPPGHDDQLWLVMEFCGAGSITDLVKNT  
KGNTLKEDWIAYSISREILRGLAHLHIHHVIHRDIKGQNVLLTENA EVKLVD FGVSAQLDR  
TVGRRNTFIGTPYWMAPEVIACDENPDATYDYRSDLWSCGITAIEMAEGAPPLCDMHPMR  
ALFLIPRNPPLRLKSKKWSKKFFSFIEGCLVKNYMQRPEQLLKHPFIRDQPNERQVRI  
QLKDHIDRTRKKRGEKDETEYEYSGSEEEEEVPEQEGEPSSIVNVPGESTLRRDFLRLQ  
QENKERSEALRRQQLLEQQRLREQEYKQQLLAERQKRIEQQKEQRRRLEEQQRREREAR  
RQQEREQRRREQEKKRRLEELERRRKEEEERRRAEEKRRVEREQEYIRRLQEEEEQRHLE  
VLQQQLLEQAMLLRCRWREMEHRQAERLQRQLQEQAYLLSLQHDHRRPHPHQSQQPP  
PPQQERSKPSFHAPEPKAHYEPADRAREVEDRFRKTNHSSPEAQSKQTGRVLEPPVPSRS  
ESFSNGNSESVHPALQRPAPQVPVRTTSRSPVLSRRDSPLQSGGQQNSQAGQRNSTSIE  
PRLWERVEKLVPRPGSGSSSGSSNSGSGPGSHPGSGSGGERFRVRSSSKSEGSPSQRL  
ENAVKKPEDKKEVFRPLKPADLTALAKELRAVEDVRPPHKVTDYSSSSSESGTTDEEDDD  
VEQEGADESTSGPEDTRAASSLNLNGETESVKTMIVHDDVESEPAMTPSKEGTLIVRRT  
QSASSTLQKHKSSSSFTPFIDPRLQLISPSSGTTVTSVVGFS CDGMRPEAIRQDPTRKGS  
VVNVNPTNTRPQSDTPEIRKYKKRFNSEILCAALWGVNLLVGTESGLMLLDRSGQGKVYP  
LINRRRFQQMDVLEGLNVLTISGKKDKLRVYYLSWLRNKILHNDPEVEKKQGWTTVGDL  
EGCVHYKVVKYERIKFLVIALKSSVEVYAWAPKPYHKFMAFKSFGELVHKPLLVDLTVEE  
GQRLKVIYSGCAGFHAVD VDSG SVYDIYLP THIQCSIKPHAIILPNTDGMELLVCYED  
GVYVNTYGRITKDVVLQWGEMPTSVAYIRSNQTMGWGEKAIEIRSVETGHLDGVMHKRA  
QRLKFLCERN DKVFFASVRSGGSSQVYFMTLGRTSLLSW

SEQ ID NO: 14 ZC2 human Nterm=missing kin=1-255 coiled-coil=256-442  
pro=443-626 B=627-954 Rab/RacBD=955-1297

AFGEVYEGRHVKTGQLAAIKVMDVTGDEEEEIKQEINMLKKYSHRNIATYYGAFIKKNP  
PGMDDQLWLVMEFCGAGSVTDLIKNTKGNTLKEEWIAYICREILRGLSHLHQHKVIHRDI  
KGQNVLLTENA EVKLVD FGVSAQLDR TVGRRNTFIGTPYWMAPEVIACDENPDATYDFKS  
DLWSLGITAIEMAEGAPPLCDMHPMRALFLIPRNPAPRLKSKKWSKKFQSFIESCLVKNH  
SQRPAEQMLMKHPFIRDQPNERQVRIQLKDHIDRTRKKRGEKDETEYEYSGSEEEEEEND  
SGEPSSILNLPRESTLRRDFLRLQLANKERSEALRRQQLLEQQRENEEHKRQLLAERQKR  
IEEQKEQRRRLEEQQRRREKELRKQQEREQRRHYEEQMRREEERRRAEHEQEYKRKQLEEQ  
RQAERLQRQLKQERDYLVS LQHQRQEQR PVEKKPLYHYKEGMSPSEKPAWAKEVEERSRL  
NRQSSPAMPHKVANRISDPNLPPRSEFSISGVQPARTPPMLRPVDPQIPHLVAVKSQGP  
ALTASQSVHEQPTKGLSGFQEALNVTSHRVEMPRQNSOPTSENPLPTRIEKFDRSSWLR

**Fig. 8B**

27/76

QEEDIPPKVPQRTTSISPALARKNSPGNGSALGPRLGSQPIRASNPDLRRTEPILESPLQ  
 RTSSGSSSSSTPSSSQSSQGGSQPGSQAGSSERTRVRANSKSEGSPVLPHEPAKVKPEE  
 SRDITRPSRPASYKKAIDEDLTALAKELRELRIEETNRPMKKVTDYSSSSEESSESEEE  
 EDGESETHDGTVAVSDIPRLIPTGAPGSNEQYNVGMVGTHGLETSHADSFSGSISREGTL  
 MIRETSGEKKRSGHSDSNGFAGHINLPDLVQQSHSPAGTPTEGLGRVSTHSQEMDSGTEY  
 GMGSSTKASFTPFVDPRVYQTSPTDEDEEDEESSAAALFTGELLRQEQAQLNEARKISVV  
 NVNPTNIRPHSDTPEIRKYKKRFNSEILCAALWGVNLLVGTENGLMLLDRSGQGKVYNLI  
 NRRRFQQMDVLEGLNVLVTISGKKNKLRVYYLSWLRNRILHNDPEVEKKQGWITVGDLEG  
 CIHYKVVKYERIKFLVIALKNAVEIYAWAPKPYHKFMAFKSFADLQHKPLLVDLTVEEGQ  
 RLKVIFGSHTGFHVIDVDSGNSYDIYTPSHIQGNITPHAIVILPKTDGMEMLVCYEDEGV  
 YVNTYGRITKDVLVQWGEMPTSVAYIHSNQIMGWGEKAIEIRSVETGHLDGVFMHKRAQR  
 LKFLCERNDKVFFASVRSGGSSQVFFMTLNRNSMMNW

SEQ ID NO: 15 ZC3 human kin=1-255 coiled-coil=256-476 pro=477-680  
 B=681-983 Rab/RacBD =984-1326

AFGEVYEGRHVKTGQLAAIKVMDVTEDEEEEIKQEINMLKKYSHHRNIATYYGAFIKKSP  
 PGNDQDLWLVMFCGAGSVTDLVKNTKGNALKEDCIAYICREILRGLAHLHAHKVIHRDI  
 KGQNVLLTENA EVKLVD FGVSAQLDRTVGRNRTFIGTPYWMAPEVIACDENPDATYDYRS  
 DIWSLGITAIEMAEGAPPLCDMHPMRALFLIPRNPPRLKSKKWSKKFIDFIDTCLIKTY  
 LSRPTEQLLKFPFIRDQPTERQVRIQLKDHIDRSRKKRGEKEETEY EYSGSEEEEDDSHG  
 EEGEPSSIMNVPGESTLRREFLRLQQENKSNSEALKQQQQQLQQQQQRDPEAHIKHLLHQR  
 QRRIEEQKEERRRVEEQRREREQRKLQEKEQQRLEDMAALRREEERRQAEREQEYIRH  
 RLEEEQRQLEILQQQLLQEQALLLEYKRKQLEEQRQSERLQRQLQEQEHAYLKSLLQQQQQ  
 QQLQKQQQQQLLPGRKPLYHYGRGMNPADKPAWAREVEERTRMNKQQNSPLAKSKPGST  
 GPEPPIPQASPGPPGPLSQTPPMQRPVEPQEGPHKSLVAHRVPLKPYAAPVPRSQSLQDQ  
 PTRNLAAFPASHDPDAIPAPTATPSARGAVIRQNSDPTSEGPGPSNPPPAWVRPDNEAP  
 PKVPQRTSSSIATALNTSGAGGSRPAQAVRARPRNSAWQIYLQRRRAERGTPKPPGPPAQP  
 PGPPNASSNPDLRRSDPGWERSDSVLPASHGHLPPAGSLERNRVGVSSKPDSSPVLSPGN  
 KAKPDDHRSRPGRPADFVLLKERTLDEAPRPPKKAMDYSSSSEEVESSEDEEEGEGGPA  
 EGSRDTPGGRDGDTDSVSTMVVDVEEITGTQPPYGGGTMMVQRTPEEERNLLHADSNGY  
 TNLDPDVVQPSHSPTENSKGQSPPSKDGSGDYQSRGLVKAPGKSSFTMFVDLGIYQPGGSG  
 DSIPITALVGGEGTRLDQLQYDVRKGSVVNVNPTNTRAHSETPEIRKYKKRFNSEILCAA  
 LWGVNLLVGTENGLMLLDRSGQGKVYGLIGRRRFQQMDVLEGLNLLITISGKRNLKRVYY  
 LSWLRNKILHNDPEVEKKQGWTTVGDMEGCGHYRVVKYERIKFLVIALKSSVEVYAWAPK  
 PYHKFMAFKSFADLPHRPLLVDLTVEEGQRLKVIYGSSAGFHAVDVDSGNSYDIYIPVHI  
 QSQITPHAIIFLPNTDGMEMLLCYEDEGVYVNTYGRIIKDVLVQWGEMPTSVAYICSNQI  
 MGWGEKAIEIRSVETGHLDGVFMHKRAQR LKFLCERNDKVFFASVRSGGSSQVYFMTLNR  
 NRIMNW

**Fig. 8C**  
 28/76

SEQ ID NO: 16 ZC4 human Nterm kin coiled-coil pro B=missing  
Rab/RacBD=1-349

NVNPLYVSPACKKPLIHMYEKEFTSEICGSLWGVNLLLGTRSNLYLMDRSGKADITKLI  
RRRPFRQIQVLEPLNLLITISGHKNRLRVYHLTWLRNKILNNDPESKRRQEMLKTEEAC  
KAIDKLTGCEHFSVLQHEETTYIAIALKSSIHLYAWAPKSFDESTAIKVFTLDHKPVTV  
DLAIGSEKRLKIFFSSADGYHLIDAEEVMSDVTLPKNPLEIIIPQNIILPDCLGIGMM  
LTFNAEALSVEANEQLFKKILEMWKDIPSSIAFECTQRTTGWGQKAIEVRSLSRVLESE  
LKRRSIKKLRFLCTRQDKLFFTSTLRNHHSRVYFMTLGKLEELQSNYDV

SEQ ID NO: 18 KHS2 human Nterm=1-13 kin=14-273 A=274-346  
Pro=347-534 RabBD =535-894

MNPGFDLSRRNPQEDFELIQRIGSGTYGDVYKARNVNTGELAAIKVIKLEPGEDFAVVQQ  
EIIMMKDCKHPNIVAYFGSYLRRDKLWICMEFCGGGSLQDIYHVTGPLSELQIAYVSRET  
LQGLYYLHSGKGMHRDIKANILLTDNGHVKLADFGVSAQITATIAKRKSFIGTPYWMAP  
EVAVERKGGYNQLCDLWAVGITAEIELAELQPPMFDLHPMRALFLMTKSNFQPPKLKDKM  
KWSNSFHHFVKMALTKNPKKRPTAEKLLQHPFVTQHLTRSLAIELLDKVNNPDHSTYHDF  
DDDDPEPLVAVPHRIHSTSRNVREEKTRSEITFGQVKFDPPLRKETEPHHELPSDGFLO  
SSEEIYYTARSNDLQLEYGQGHQGGYFLGANKSLLKSVEEELHQRGHVAHLEDDEGDDD  
ESKHSTLKAKIPPLPPPKKSIFIPQEMHSTEDENQGTIKRCPMMSGSPAKPSQVPPRPPP  
PRLPPHKPVALGNMSSFQLNGERDGSQCQQNEHRGTNLSRKEKKDVPKPISNGLPPTP  
KVHMGACFSKVFNGCPLKIHCASSWINPDTRDQYLIFGAEEGIYTLNLNELHETSMEQLF  
PRRCTWLYVMNCLLSISGKASQLYSHNLPGLFDYARQMQLPVAIPAHLKLPDRILPRKF  
SVSAKIPETKWCQKCCVVRNPYTGHKYLCAALQTSIVLLEWVEPMQKFMLIKHIDFPIPC  
PLRMFEMLVVPEQEYPLVCVGVSRGRDFNQVVRFETVNPNSTSSWFTESDTPQTNVTHVT  
QLERDITLVCLDCCIKIVNLQGRKSSRKLSELTFDFQIESIVCLQDSVLAFWKHGMQG  
RSFRSNEVTQEISDSTRIFRLGSDRVVLESRPTDNPTANSNLYILAGHENSY

SEQ ID NO: 22 SULU1 human N=1-21 kin=22-277 A=278-427  
coiled-coil1=428-637 B=638-751 coiled-coil2=752-898

MRKGVLDKDEIDDLFYKDDPEELFIGLHEIGHGSFGAVYFATNAHTNEVVAIKKMSYSGK  
QTHEKWQDILKEVKFLRQLKHPNTIEYKGCYLKEHTAWLVMYCLGSASDLLEVHKKPLQ  
EVEIAAITHGALHGLAYLHSHALIHRDIKAGNILLTEPGQVKLADFGSASMASPANSFVG  
TPYWMAPEVILAMDEGQYDGKVDIWSLGITCIELAERKPPLFNMNAMSALYHIAQNDSP  
LQSNWTDSEFRFVDYCLQKIPQERPTSAELLRHDFVRRDRPLRVLIDLIQRTKDAVREL  
DNLQYRKMKKILFQETRNGPLNESQEDEEDSEHGTSLNREMSLGSNHSIPSMVSTGSQ  
SSSVNSMQEVMDESSSELVMMHDESTINSSSVVHKKDHVFTRDEAGHGDPPEPRPTQ  
SVQSQUALHYRNRERFATIKSASLVTRQIHEHEQENELREQMSGYKMRQRHQKQLIALEN  
KLKAEMDEHRLKLQKEVETHANSSIELEKLAKQVAIEKEAKVAAADEKKFQQQILAQ

**Fig. 8D**

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QKKDLTTFLESQKKQYKICKEKIKEEMNEDHSTPKKEKQERISKHKENLQHTQAEAAAHL  
 LTQQRLYYDKNCRFFKRRKIMIKRHEVEQQNIREELNKKRTQKEMEHAHLIRHDESTRELE  
 YRQLHTLQKLRLMDLIRLQHQTLENQLEYNKRRELERHRKHVMGLRQQPKNLKAMEMQIK  
 KQFQDTCKVQTKQYKALKNHQLEVTPKNEHKTILKTLKDEQTRKLAITLAEQYEQSINEMM  
 ASQALRLDEAQAECQALRLQLQQEMELLNAYQSKIKMQTEAQHERELQKLEQRVSLRRA  
 HLEQKIEEELAALQKERSERIKNLLERQEREIETFDMESLRMGFGNLVTLDFPKEDYR

SEQ ID NO: 23 SULU3 human Nterm=missing kin partial=1-66 A=67-215  
 coiled-coil1=216-425 B=426-539 coiled-coil2=540-786 Ctail=687-786  
 IELAERKPPLFNMNAMSALYHIAQNESPTLQSNEWSDYFRNFVDSCLQKIPQDRPTSEEL  
 LKHIFVLRERPETVLIDLIQRTKDAVRELDNLQYRKMKKLLFQEAHNGPAVEAQEEEEEQ  
 DHGVGRTGTVNSVGSNQSIPSMSSISASSQSSSVNSLPDVSDDKSELDMMEGDHTVMSNSS  
 VIHLKPEEENYREEGDPRTASDPQSPQVSRHKSHYRNREHFATIRTSASLVTRQMQEHE  
 QDSELREQMSGYKRMRRQHQQKQKQMTLENKLKAEMDEHRLRLDKDLETQRNFAAEMEKL  
 KKHQAAMEKEAKVMSNEEKKFQQHIQAQQKELNSFLESQKREYKLRKEQLKEELNENQS  
 TPKKEKQEWLSKQKENIQHFQAEAAANLLRRQRQYLELECRRFKRRMLLGRHNLEQDLVR  
 EELNKRQTQKDLHAMLLRQHESMQELEFRHLNTIQKMRCELIRLQHQTETLNQLEYNKR  
 RERELRRKHVMEVRQQPKSLKSKELQIKKQFQDTCKIQTRQYKALRNHLLLETPKSEHKA  
 VLKRLKEEQTRKLAITLAEQYDHSINEMLSTQALRLDEAQAECQVLKMQQLQEELELLNAY  
 QSKIKMQAQAHDRELRELEQRVSLRRALLEQKIEEMLALQNERTERIRSLLERQAREI  
 EAFDSESMRLGFSNMVLSNLSPEAFSHSYPGASGWSHNPTGGPGPHWGHMGGPPQAWGH  
 PMQGGPQPGWHPSGPMQGVPRGSSMGVRNSPQALRRRTASGGRTAQGMSRSTSVTSQISNG  
 SHMSYT

SEQ ID NO: 24 SULU3 murine Nterm=1-25 kin=26-273 A=274-422  
 cc1=423-632 B=633-748 cc2=missing  
 MPSTNRAGSLKDPEIAELFFKEDPEKLFTDLREIGHGSFGAVYFARDVRTNEVVAIKKMS  
 YSGKQSTEKWQDIIEVKFLQRIKHPNSIEYKGCYLREHTAWLVMEYCLGSASDLLEVHK  
 KPLQEVEIAAITHGALQGLAYLHSHTMIHRDIKAGNILLTEPGQVKLADFGSASMASPAN  
 SFVGTPTYWMAPEVILAMDEGQYDGKVDVWSLGITCIELAERKPPLFNMNAMSALYHIAQN  
 ESPTLQSNMNDSCCLQKIPQDRPTSEELLKHMFLRERPETVLIDLIQRTKDAVRELDNLQ  
 YRKMKKLLFQEAHNGPAVEAQEEEEEQDHGVGRTGTVNSVGSNQSIPSMSSISASSQSSSV  
 NSLPDASDDKSELDMMEGDHTVMSNSSVIHLKPEEENYQEEGDPRTASDPQSPQVSRH  
 KSHYRNREHFATIRTSASLVTRQMQEHEQDSELREQMSGYKRMRRQHQQKQKQMTLENKLKAE  
 MDEHRLRLDKDLETQRNFAAEMEKLKKHQAAMEKEAKVMAEKKFQQHIQAQQKEL  
 NSFLESQKREYKLRKEQLKEELNENQSTPKKEKQEWLSKQKENIQHFQAEAAANLLRRQR  
 QYLELECRRFKRRMLLGRHNLEQDLVREELNKRQTQKDLHAMLLRQHESMQELEFRHLN  
 TIQKMRCELIRLQHQTETLNQLEYNKRRELERRRKHVMEVRQQPKSLKSKELQIKKQFQD

**Fig. 8E**

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TCKIQTRQYKALRNHLLLETPKNEHKAI

SEQ ID NO: 26 GEK2 human N=1-33 kin=34-294 A=295-337 B=338-472 215  
coiled-coil1=473-724 215 coiled-coil2=725-912

MAFANFRRILRLSTFEKRKSREYEHVRRDLDPNEVWEIVGELGDGAFGKVYKAKNKETGA  
LAAAKVIETKSEEELEDYIVEIEILATCDHPYIVKLLGAYYHDGKLWIMIEFCPGGAVDA  
IMLELDRLTEPQIQVVCQMLEALNFLHSKRRIHRDLKAGNVLMTLEGDIRLADFGVSA  
KNLKTQLQRDSFIGTPYWMapevVMCETMKDTPYDYKADIWSLGITLIEMAQIEPPHEL  
NPMRVLLKIAKSDPPTLLTPSKWSVEFRDFLKIALDKNPETRPSAAQLLEHPFVSSITSN  
KALRELVAEAKAEVMEEIEDGRDEGEEEDAVDAASTLENHTQNSSEVSPPSLNADKPLEE  
SPSTPLAPSQSQDSVNEPCSQPSGDRSLQTTSPPVVAPGNENGLAVPVPLRKS RVPVSM DA  
RIQVAQEKQVAEQGGDLSPAANRSQKASQSRPNSSALETLGGEKLANGSLEPPAQAAAGP  
SKRSDSCSSLCTSESMDYGTNLSTDLNLKEMGSLSIKDPKLYKKT LKRTRKFVVDGVEV  
SITTSKIISEDEKKDEEMRFLRRQELRELRLLLQKEEHRNQTQLSNKHELQLEQMHRFEQ  
EINAKKKFFDTELENLERQQKQVEKMEQDHAVRRREEARRIRLEQDRDYTRFQEQLKLM  
KKEVKNEVEKLPRQQRKESMKQMEEHTQKKQLLDRDFVAKQKEDLELAMKRLTTDNRR  
ICDKERECLMKKQELLRDREAALWEMEEHQLQERHQLVKQQLKDQYFLQRHELLRKHEKE  
REQMQRYNQRMIEQLKVRQQQEKARLPKIQRSEGKTRMAMYKSLHINGGGSAAEQREKI  
KQFSQQEEKRQKSERLQQQKHENQMRDMLAQCESNMSELQQLQNEKCHLLVEHETQKLK  
ALDESHNQLKE

SEQ ID NO: 29 PAK4 human Rac=1-51 A=52-224 Nterm=225-393  
kin=394-658 Ctail=659-681 residues 13-23

(SAPQNFQHRVH)= Cdc42 /Rac-binding motif

MFRKKKKKRPEISAPQNFQHRVHTSFDPKEGKFVGLPPQWQNILDTLRRPKPVVDPSRIT  
RVQLQPMKT VVRGSAMPVDGYISGLLNDIQKLSVISSNTLRGRSPTSRRRAQSLGLLGDE  
HWATDPD MYLQSPQSERTDPHGLYLSCNGGTPAGHKQMPWPEPQSPRVLPNGLA AKAQSL  
GPAEFQ GASQRCLQLGACLQSSPPGASPTGTNRHGMKA AKHGSEEARPQSCLVGSATGR  
PGGEGSPSPKTRESSLKRRLFRSMFLSTAATAPPSSSKPGPPPQSKPNSSFRPPQKDNPP  
SLVAKAQLPSDQPVGTFSPLTTSDTSSPQKSLRTAPATGQLPGRSSPAGSPRTWHAQIS  
TSNLYLPQDPTVAKGALAGEDTGVVTHEQFKAALRMVVDQGDPRLLDSYVKIGEGSTGI  
VCLAREKHSGRQVAVKMMDLRKQQRRELLFNEVVIMRDYQHFNVVEMYKSYLVGEELWVL  
MEFLQGGALTDIVSQVRLNEEQIATVCEAVLQALAYLHAQGV IHRDIKSDSILLTLDGRV  
KLSDFGFCAQISKDVPKRKSLVGTPYWMapevISRSLYATEVDIWSLGIMVIEMVDGEPP  
YFSDSPVQAMKRLRDSPPPKLKNSHKVSPLVRDFLERMLVRDPQERATAQELL DHPFLQ  
TGLPECLVPLIQLYRKQTSTC

**Fig. 8F**  
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SEQ ID NO: 30 PAK5 human Rac A=missing Nterm partial=1-114  
kin=115-379 Ctail=380-398  
ASGAKLAAGRPFNTYPRADTDHPSRGAQGEPHDVAPNGPSAGGLAIPQSSSSSSSRPPTRA  
RGAPSPGVLGPHASEPQLAPPACTPAAPAVPGPPGPRSPQREPQRVSHEQFRAALQLVVD  
PGDPRSYLDNFIKIGEGSTGIVCIATVRSSGKLVAVKKMDLRKQQRRELLFNEVVIMRDY  
QHENVVEMYNSYLVGDELWVVMFLEGGALTDIVTHTRMNEEQIAAVCLAVLQALSVLHA  
QGVIHARDIKSDSILLTHDGRVKLSDFGFCAQVSKEVPRRKSLVGTPYWMAPELISRLPYG  
PEVDIWSLIGIMVIEMVDGEPPYFNEPPLKAMKMIRDNLPPRLKNLHKVSPSLKGFLDRLL  
VRDPAQRATAAELLKHPFLAKAGPPASIVPLMRQNRTR

**Fig. 8G**



SEQ ID NO: 1 STLK2 HUMAN

TAACAGCCCACCTCCTAGCCCCGGGCTACGCGCCGCCAGCCCAGTAACCCCACTTTTGTG  
TGTCCTCCCAGGCCCCGATCGAAAAGCCTGGGAGGGCCGCCGAACCTACCCCGGAGGGAG  
GAGCCAGTCCGAACCCAAGGCGCCACCGCCGAGAAGCGGAGCGAGGCAGCATTTCGCCTC  
CATGGCCCCACTCGCCGGTGGCTGTCCAAGTGCCTGGGATGCAGAATAACATAGCTGATCC  
AGAAGAACTGTTCAAAAATTAGAGCGCATTGGGAAAGGCTCATTTGGGGAAGTTTTCAA  
AGGAATTGATAACCGTACCCAGCAAGTCGTTGCTATTAAAATCATAGACCTTGAGGAAGC  
CGAAGATGAAATAGAAGACATTAGCAAGAAATAACTGTCTTGAGTCAATGTGACAGCTC  
ATATGTAACAAAATACTATGGGTCATATTTAAAGGGGTCTAAATTATGGATAATAATGGA  
ATACCTGGGCGGTGGTTCAGCACTGGATCTTCTTCGAGCTGGTCCATTTGATGAGTTCCA  
GATTGCTACCATGCTAAAGGAAATTTTAAAGGTCTGGACTATCTGCATTAGAAAAGAA  
AATTCACCGAGACATAAAAGCTGCCAATGTCTTGCTCTCAGAACAAAGGAGATGTTAAACT  
TGCTGATTTTGGAGTTGCTGGTCAGCTGACAGATACACAGATTAAAAGAAATACCTTTGT  
GGAACTCCATTTTGGATGGCTCCTGAAGTTATTCAACAGTCAGCTTATGACTCAAAAGC  
TGACATTTGGTCATTGGGAATTACTGCTATTGAACTAGCCAAGGGAGAGCCACCTAACTC  
CGATATGCATCCAATGAGAGTTCTGTTTCTTATTCCCAAAAACAATCCTCCAACCTCTGT  
TGGAGACTTTACTAAGTCTTTTAAGGAGTTTATTGATGCTTGCCTGAACAAAGATCCATC  
ATTTGTCCTACAGCAAAAGAACTTCTGAAACACAAATTCATTGTAAAAAATTCAAAGAA  
GACTTCTTATCTGACTGAACTGATAGATCGTTTTAAGAGATGGAAGGCAGAAGGACACAG  
TGATGATGAATCTGATTCCGAGGGCTCTGATTCCGAATCTACCAGCAGGGAAAACAATAC  
TCATCCTGAATGGAGCTTTACCACCGTACGAAAGAAGCCTGATCCAAAGAAAGTACAGAA  
TGGGGCAGAGCAAGATCTTGTGCAAACCTGAGTTGTTTGTCTATGATAATCACACCTGC  
ATTTGCTGAACTTAAACAGCAGGACGAGAATAACGCTAGCAGGAATCAGGCGATTGAAGA  
ACTCGAGAAAAGTATTGCTGTGGCTGAAGCCGCCTGTCCCGGCATCACAGATAAAATGGT  
GAAGAACTAATTGAAAAATTTCAAAGTGTTGAGCAGACGAATCCCCCTAAGAACTTA  
TTATTGGCTTCTGTTTCATATGGACCCAGAGAGCCCCACCAAACCTACGTCAAGATTAAC  
AATGCTTAACCCATGAGCTCCATGTGCCTTTTGGATCTTTGCAACACTGAAGATTTGGAA  
GAAGCTATTAACTATTTTGTGATGGCGTTTATCATTTTATATTTTGAAGGATTATTTT  
GTAAGGAATAACTTTTAATACTATAGTTTACCTGTATTCTAGTAAATGTTGAGACACCG  
TTTTGCTTTTAAGTATCCCTATTTCTTAAGTTACGAGGATGAATACCTTTACATTTTGA  
TCTTTAGTTGACTCTACAGTCATGAAACATACAGGTCTTTCAAAGTCATTCTCAATATTC  
AGCTTTTGTAAATTATCAAGCTTCAAAAAGCTTTTTTTTTAAAAAACAATGCATATT  
CTAAAAATGACTATTGGTGGGGAGGTGTAAATAAGTCATACCTTCTTAAACAGAAAATT  
TAAGTAAAGTCTTTTAAATGAAACCTGTAAAGTATTGACTCTTCTACCAAGTTGGTATG  
ATATTCAGGCAGCTCAATGATTATCACATTTGAGACCCTGTGTTTGAAGCATTACAGG  
CAATGTACAGCAACAGAGGTACCTCTTGGTGTATAGTATTTACATTCTCTTTTAGGTAGA  
AGAGGCAATTTTACCCTTATTTACATGGTTAGAAATTTAAAGCAAGATCATTTACCCAA

**Fig. 9A**

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GGATAGGTGTTTGGTAATGTTGAAGGAGTTAGTCTGGCTTCATGTTTTACATCTTCAACT  
AAAATCCCATACTATCTGCTTGGATTTGGAGAGCCAAAAAATAAAGCTGATTGTCATGTG  
ATTAAATATCTGATCAACAGGTATGAATATAACTTAAATCAGCATATTTTTGCCATGGTA  
ATAAATTGTCCTATAAACTATTTATATATTTTTGTTCTTCATAATTATCACTAATAAGCA  
TCAGTTTGTGTTTTTAAAAGGATATTTAAGTGAGCATTCTTAGTTTCATATGAAAATAA  
CCATAGTACAGGATGATTTCTGTCCACACAAAGGTTAAATTAGATTGCACAGTTAATTTT  
CACTTATATTTATGGTACTATTATGTGGGTGATGCCTTTTTCTTTTAAGCCCAGTACATA  
TATTATGCCTGCCTAAGTCTGAAGTGGGGCTGTATTTTCAGTAGTTGTAGAATTATTGAT  
ATTTAGTTTTGATAGCTAATGTTTAATTGTTTGGATCTGCACAGTTTGGTTTTTGCACAA  
AAGTCATTTAAAAAATCTGAGTAATTGTCAAATATTAAGAAAGATATTCTTCCTGTA  
AGGAATACAGTTTTTGTAGTCAAAGTGGCCATTACATCCTCTTTTAATTTACATAATACAG  
ATACTTGAGAAAGTTGTTGTGGTGTGTATGCCAAGAAAATTCTTTTTATTGGTGCCTAT  
ATTGTAACAATTATTTTTAATGCATTGTATTTTGAAGTAACGGTTCAGTTAAATTTTTCA  
CCTGCTGTGTAAGTGAACACAATTACAGTTTATAATCATCTGTAGAAGTCTGGAGATAA  
TTTTGCAACTCATGTTATGGGTAAATGAATATTTTTGTAAAAGTAAAAGCAACAAATTT  
ATAAATTGATTATTTGAACTTTACAACACAATTGCATCCCAAATACAAATTGTATTGCT  
TATTCATTATAGCTATTCGTCCTGTAATCTGTTTCTAGGTGAAGCATACTCCAGTGTTTT  
AGGGGTTTTGAAAATAAATATTTAAATTTACAGTCAAAAAAAAAAAAAAAAAAAAAA  
AAAAAAAAAAAAAAAAAAAAAAAAAAAA

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GACAGCAGCGCCGGCCCCGGCAGCTCCCGCGGCCCCGGCCCCGGCCCCGGCCCCGGCCCC  
GGCGGCACAGGCTGTGCGCTGGCCCATCTGCAGGGACGCGTACGAGCTGCAGGAGGTTAT  
CGGCAGTGGAGCTACTGCTGTGGTTCAGGCAGCCCTATGCAAACCCAGGCAAGAACGTGT  
AGCAATAAAACGGATCAACTTGGAAAAATGCCAGACCAGTATGGATGAACTATTAAGA  
AATTCAAGCCATGAGTCAGTGCAGCCATCCCAACGTAGTGACCTATTACACCTCTTTTGT  
GGTCAAAGATGAACTTTGGCTGGTCATGAAATTACTAAGTGGAGGTTCAATGTTGGATAT  
CATAAAATACATTGTCAACCGAGGAGAACACAAGAATGGAGTTCTGGAAGAGGCAATAAT  
AGCAACAATTCTTAAAGAGGTTTTTGAAGGCTTAGACTATCTACACAGAAACGGTCAGAT  
TCACAGGGATTTGAAAGCTGGTAATATTCTTCTGGGTGAGGATGGTTCAGTACAAATAGC  
AGATTTTGGGGTAAGTGCCTTCTAGCAACAGGGGGTGATGTTACCCGAAATAAAGTAAG  
AAAAACATTCGTTGGCACCCCATGTTGGATGGCTCCTGAAGTCATGGAACAGGTGAGAGG  
CTATGACTTCAAGGCTGACATGTGGAGTTTTTGAATAACTGCCATTGAATTAGCAACAGG  
AGCAGCGCCTTATCACAAATATCCTCCCATGAAAGTGTTAATGTTGACTTTGCAAAATGA  
TCCACCCACTTTGGAAACAGGGGTAGAGGATAAAGAAATGATGAAAAGTACGGCAAGTC  
CTTTAGAAAATTACTTTCACTGTGTCTTCAGAAAGATCCTTCCAAAAGGCCACAGCAGC  
AGAAGTTTTAAATGCAATTCTTCAGAAAGCCAAGAACAGAGAGTACCTGATTGAGAA  
GCTGCTTACAAGAACACCAGACATAGCCCAAGAGCCAAAAGGTAAGAAGAGTTCCTGG

**Fig. 9B**

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GTCAAGTGGTCACCTTCATAAAACCGAAGACGGGGACTGGGAGTGGAGTGACGACGAGAT  
GGATGAGAAGAGCGAAGAAGGGAAAGCAGCTTTTTCTCAGGAAAAGTCACGAAGAGTAAA  
AGAAGAAAATCCAGAGATTGCAGTGAGTGCCAGCACCATCCCCGAACAAATACAGTCCCT  
CTCTGTGCACGACTCTCAGGGCCCACCCAATGCTAATGAAGACTACAGAGAAGCTTCTTC  
TTGTGCCGTGAACCTCGTTTTGAGATTAAGAACTCCAGAAAGGAACTTAATGACATACG  
ATTTGAGTTTACTCCAGGAAGAGATACAGCAGATGGTGTATCTCAGGAGCTCTTCTCTGC  
TGGCTTGGTGGATGGTCACGATGTAGTTATAGTGGCTGCTAATTTACAGAAGATTGTAGA  
TGATCCCAAAGCTTTAAAAACATTGACATTTAAGTTGGCTTCTGGCTGTGATGGGTCCGA  
GATTCCTGATGAAGTGAAGCTGATTGGGTTTGCTCAGTTGAGTGTCAGCTGATGTATGTC  
CCTTGATGTCACCCTGATCTGTCTATGCCCCACCGCCACCCCTACTCCCTTCAACCCTCCC  
TCTTTCTGCCATTTCTCCACCCCTCACTCCCATTTCTAGCAAAATCAGAAGATTG  
TGAAGAGGCCGGCTTCAACAAAATGGGATAAAAAAATAATTTTTTAAACTTACAACACT  
CCGAGTTCTGCTTTATTCTCTAGCAATCCACAGTACAAGAACAAGCAAATGCCACAGCTG  
CACGACTGTTGCTCATTTTTCCAAAAGCTATTTAATATTCTTAGCAATCAATTTGGATAT  
CCCTTAAGTGAAGAATCTGAAATACACTCAGGTGGTCTTATTTATTGGCAACAAAAGG  
AATTTTCTATCCAGAAGCCTATTTCTCCTTTCATTGTTGTTATTTCTGTTATAATACTTT  
AATTGTACATCTGACAATACTGCCTCTTTTATGTTGTATTTAGAAATTAATATACTTATA  
AAATTAAGATTTATTAGCCAACTTGAATTCTAGTTTTTAAACTGACTGTGAATTTTATT  
TTTCATATATTTATGCATTACACACCTTAGCTATAAGAAAAAAGGGTTTTGATTATATG  
CTTCTTGCAGTTAATCTCGTTATTTAAACAAAAAGTTTTGGGTCTATCTTTGGAGTATTT  
GTAACCTCTAAATTTTGAATGACTGAATTAGGAATTTGGATGCTTATTCTTTTAGTCTG  
TTTGCCTAAAAACCAATTTACAATCTGACTGTCTCTTGGGAGAGGGAGGTGCCTTGCAAA  
CTTTCACATTAAGAATGTGCCTGAGGCTGCTTACTCTGGAATAGTCTCAGATCTAAAT  
TTCCTCTATATAAGGTGGCATATGTAAAGTTTTGCTTCATTGGACCGTTTAGAATGCTAT  
GTAAATGTTGCCATTCTGTTAGATTGCTAACTATATACCCATCTCTGATTTGGCTCTCC  
TTAAGTGATAGGATTTGTTATTCTAAAGGTGATAAACTTGAAAAATATCAGAATCTGAGTT  
TTACTTGAAATTTTGCAGAATACCCAGGTGGAGTGAAAATTGGAAGGGTTTTGTGCAATG  
ACTAAAAGGTAAAACGCTGTAAAGGTTCAAGAATCAATACTTTCAACCCAAGTAGCCCTC  
TGCTTGACTGTATATTATGGAAGTAGTAAACCTTAGGATTTTGAAAATTGGAGTCTAATC  
TTTCAAGGAGGTGGGCTCCCAGGATGGTACCATTGCTCTTTCCTAGCTAACCTAGATAT  
GGCAGCTCTTTAATGTACTTCAAAAAGCAAATATATATTACTAAGGAAAAAAGTTATTT  
ATAATTGCCTTGTACATAATTGTTAAGGTGTTCTAGAGCCATTTGCATACAATTTAATGTA  
ATTTCAATTCATTCTATTGTTTACACAACGATTACTCGAAGATGACTGCAAAGGTAAAAG  
GAAAATAAAAAGTGTATTGCACAATGAAAAA

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CAAAAGTGGAGTCCTAGATGANTCTACCATTGCTACGATACTCCGAGAAGTACTGGAAGG  
GCTGGAATATCTGCATAAAANTGGACAGATCCACAGAGATGTGAAAGCTGGAACATTCT

**Fig. 9C**  
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TNTTGGAGAAGATGGCTCAGTACAGATTTTACAGACTTTGGGGTTAGTGCTTTTTTAGCAAC  
TGGTGGTGATATTACCCGAAATAAAGTGAGAAAGACCTTTGTTGGCACCCCTTGTTGGAT  
GGCACCTGAAGTTATGGAACAGGTCCGTGGTTATGATTTCAAAGCTGATATTTGGAGTTT  
TGGAAATTACAGCAATTGAATTGGCTACAGGGGCGGCTCCTTATCATAAATATCCACCAAT  
GAAGGTTTTAATGCTGACACTGCAGAACGATCCTCCTTCTTTGGAAACTGGTGTTCAAGA  
TAAAGAAATGCTGAAAAAATATGGAAAATCATTTAGAAAAATGATTTTATTGTGCCTTCA  
AAAAGATCCAGAAAAAAGACCAACAGCAGCAGAACTATTAAGGCACAAATTTTTCCAGAA  
AGCAAAGAATAAAGAATTTCTTCAAGAAAAAACATTGCAGAGAGCACCAACCATTCTGA  
AAGAGCAAAAAAGGTTCCGGAGAGTACCAGGTTCCAGTGGGCGTCTTCATAAGACAGAGGA  
TGGAGGCTGGGAGTGGAGTGATGATGAATTTGATGAAGAAAGTGAGGAAGGGAAAGCAGC  
AATTTACAACTCAGGTCTCCCCGAGTGAAAGAATCAATATCAAATTCTGAGCTCTTTCC  
AACAACTGATCCTGTGGGTACTTTGCTCCAAGTTCAGAACAGATCTCTGCTCATCTACC  
TCAGCCAGCTGGGCAGATTGCTACACAGCCAACTCAAGTCTCTCTCCACCCACCGCAGA  
GCCAGCAAAAACAGCTCAGGCTTTGTCTTCAGGATCAGGTTTACAAGAAACCAAGATCCC  
AATCAGTCTAGTACTAAGATTAAGGAATTCCAAAAAGAACTAAATGATATTCGATTTGA  
ATTTACTCCTGGGAGAGATACAGCAGAGGGTGTCTCTCAGGAACCTATTTCTGCTGGCCT  
GGTCGACGGAAGGGATTTAGTAATAGTGGCAGCTAATTTGCAGAAAATTGTGGAAGAACC  
TCAGTCAAATCGATCTGTCACTTTCAAACCTGGCATCTGGTGTGGAAGGCTCAGATATTCC  
TGATGATGGTAAACTGATAGGATTTGCCAGCTCAGCATCAGCTAAACCACAACCCCTGGA  
AGAGGCGGCCTAAGGAGATTCCACACATGCGTATCTCTGTTGCTTCTATTGGCCTAAACC  
CACTACTGCCAAAGAACCCAGCAACAAACCTCCCGGCTAGGAGCTTTAGAAGTCTTTATG  
TTCTTCTGCCATCATTCTCTTTTCCACAGGGAAAGAAAAGTTGGATCACTAGTGGC  
CAGCATCCCCAGAGTTCGGTTAGTAACTTACTTCATATGTCCCCTGTCTTCTCCATCT  
GAGAAGTGGCCCATGTGCTTCAAGGCCAGGAGGGAGATCTGTCAGCTCATTCTTGCCTT  
ACTCCAATGATGGCCCAGGTGGAAAAGTAGCAGCTGTATCGGGCTTCTCATCTGCCTG  
TTCCCCACACCTGCCAGGATATGGACATCTTGGGATATCTCTTTACCACTGAAGTAGAA  
TTGATTGTTTCAGCTGGAGCCCAGAGAATTTAATTTAATGTTTTTTCTTTGTACCTGATGT  
GAATTCTAGCAACCTTTGTTAGGAAAAAGCACAGCCTCAGATGGAGGCAGCCTAAACTGT  
GTTCTTGTTTTGTTTCATGGTGTCTTAAGCGTTTTGCTGAAGCTGCTCTCAGGCACCCCC  
TTCTTCATTGCTCTCTCCAGAAAGGGTTGCTAGCCTTAACTTCAGCTGGTGCAAAACATC  
TGACTGTAGCCGAACCTCAGCCATCAGATCCTTCAAAGTGGAACCTTTGGATTGTTTTTAC  
AGACAACATCGAGTAATGGCTTGTAATGTGAATTTTCCAGAGGTGGTTTTTGAACAGG  
AAAATCATAATTCATATCATTGGAGAAGTATTTATTTTCAAATATCAAATTGAAGAAAAA  
CTCAATCCTCCCATGAAAATCAGTTCGCCTGGCCTCCAAGTCGTGAGGAAATGGGTATGC  
AAGGCTGAGATTTCTACAGCAATAAAGGAGACACACACTGGGCCAGAGAGGCCTGCCTTC  
TGCCTGCTCTCCTGCACTGACCCTTTGGAGGGGGTCTCTGTGTGCTGAAGCTAACTCAAG  
ATGGAAAGTGAAACCACATGTGCCGTGACCTTTAGGTTTTATGAGTAGACAGTGTTTATT  
TGATTTTCTACAGAAATAATAAATTATTCTTTAGGTTTAAAAAAGAGCACTCATAATG

**Fig. 9D**

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CAATATGTGAATAATCAGTGAGGTTGATTTTTCTTTTTCTTACCCTTTCATAGTCTTTG  
TCTAACTGCTAGTAACCTACCGAGTTTTATATATGAGTGGGATACTCAATCTGGCCTTA  
AAAAGATACACAAAGATGGGCTGTGGGTCCCTGGAAAGGGGAGAGTTGCCCTTTACAGA  
ATCACTCGAGCCCTTTCCAGCACTGTTGGTCTGATGAACAAGGTTGTTTTACCTTATTTT  
CTCTTGGAACATATCTGAAAACCTTCCCCACAAATAACTTGTACACCTTTTGTTCATT  
CTGAGTCTTTAGTTTTAGTCATGGGCTTTCTTCACCTGCTCTAGGTGCAAAGGCATGTTG  
GGAAAGAGATGGATGTTGGGGAGGAAGAGAGGAGATGGATTTTCAGTTGGGAGTTAGGAGG  
AGAGTAGGTGAGATGATCAGACACCGGAGTTCAACGTCCCAGCAGTCTTGGTAAAAGGAG  
GGAGCCTGCTGAGCCAGGAGGGAGAAAAGAAGATTGACCAGCTTGCTAGAAAAATACTTA  
GCTTTTCTTTTTCTTTTTTGTGGAGGGGGACGGAGAGGAACAAGGATGGGGAGGTAGG  
AATGAGGTATAGAAAAGAGATAGCATCTTCTTTGGCACAAGACTAGTGGCTTACCGCTTA  
CCTTAGAGTTTTGTTTTTTTTTTTTTCAAACCCATCAAAATCTACTTATTTATGAATCCAA  
GGGTGGCAGCATCACTCTGTTCTAGCATTCTTTGTGGAGATGGTCTGGTGCCTAGCTGG  
GAGTGAGCAGCAGCCCATCCCTGTTCACTTTCTCTAGCCCATCATTACCTGTGAAGTGC  
AGTGGGGCAGTCATGGCAAATAGAATTGGGCTGGGGTTTCTCCTTCTTTTCAGTTCATTG  
TTTGCCCTGCTAGGAATTAGAAGACAGACACCATGTCCCAGGACAGTGTTACTTCTTCTG  
CATGATGTGTGGTAGACTCCCTTTGCTGGCTTGTGCAGTGATACTGAGAAAATACATGAA  
CAGAACTGCCCAGGTGGAACAGCACGTAACCTAGTGAGTGACTGTACTCTTTCTAGGA  
ATGCTGATTCAGAGTGCACCTCTTTGACTAGGTCCCAGGATCCCCTTGTCCCTGGAGTAG  
GGACTAACTATAGCACAAAGTAATATGTGCCAATGCTATTTGTGAAATGTTTGGTCTTTC  
TAAACGACTAAAGGATTTGTTGGGTTTTTGTCTTAAGTTTTGAACCAAATCCTAGAGCCAG  
CTGATAATATTTAATAATCTGGAGGAGAGAATAATGATGTACCAATAAGTGGAGATTCTT  
CCTTATGATGTATGCTAGGTTATGGAAGATGTAAAATATTCAACTTTTTCTCCTTTTTT  
TGGACTTTGTATTTTACTGCATGTTTTCTTCATTTTAAATCAATAAAGAGTAAATTGTCA  
AAAAAAAAAAAAAAAAA

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CTCATCTGTACACACTTCATGGATGGCATGAATGAGCTGGCGATTGCTTACATCCTGCAG  
GGGTGCTGAAGGCCCTCGACTACATCCACCACATGGGATATGTACACAGGAGTGTCAA  
GCCAGCCACATCCTGATCTCTGTGGATGGGAAGGTCTACCTGTCTGGTTTGGCAGCAAC  
CTCAGCATGATAAGCCATGGGCAGCGGCAGCGAGTGGTCCACGATTTTCCCAAGTACAGT  
GTCAAGGTTCTGCCGTGGCTCAGCCCCGAGGTCTCCAGCAGAACTCTCCAGGGTTATGAT  
GCCAAGTCTGACATCTACAGTGTGGGAATCACAGCCTGTGAACTGGCCAACGGCCATGTC  
CCCTTTAAGGATATGCCTGCCACCCAGATGCTGCTAGAGAACTGAACGGCACAGTGCCC  
TGCTGTGGATACCAGCACCATCCCCGCTGAGGAGCTGACCATGAGCCCTTCGCGCTCA  
GTGGCCAACCTCTGGCCTGAGTGACAGCCTGACCACCAGCACCCCCCGGCCCTCCAACGGT  
GACTCGCCCTCCCACCCCTACCACCGAACCTTCTCCCCCACTTCCACCACTTTGTGGAG  
CAGTGCCCTTCAGCGCAACCCGGATGCCAGGCCAGTGCCAGCACCTCCTGAACCACTCT

**Fig. 9E**  
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TTCTTCAAGCAGATCAAGCGACGTGCCTCAGAGGCTTTGCCC GAATTGCTTCGTCCTGTC  
ACCCCCATACCAATTTTGAGGGCAGCCAGTCTCAGGACCACAGTGGAATCTTTGGCCTG  
GTAACAAACCTGGAAGAGCTGGAGGTGGACGATTGGGAGTTCTGAGCCTCTGCAAACCTGT  
GCGCATTCTCCAGCCAGGGATGCAGAGGCCACCCAGAGGCCCTTCTGAGGGCCGGCCAC  
ATTCCCGCCCTCCTGGGCAGATTGGGTAGAAAGGACATTCTTCCAGGAAAGTTGACTGCT  
GACTGATTGGGAAAGAAAATCCTGGAGAGATACTTCACTGCTCCAAGGCTTTTGAGACAC  
AAGGGAATCTCAACAACCAGGGATCAGGAGGGTCCAAAGCCGACATTCCCAGTCCTGTGA  
GCTCAGGTGACCTCCTCCGCAGAAGAGAGATGCTGCTCTGGCCCTGGGAGCTGAATTCCA  
AGCCCAGGGTTTGGCTCCTTAAACCCGAGGACCGCCACCTCTTCCCAGTGCTTGCGACCA  
GCCTCATTCTATTTAACTTTGCTCTCAGATGCCTCAGATGCTATAGGTCAGTGAAAGGGC  
AAGTAGTAAGCTGCCTGCCTCCCTTCCCTCAGACCTCTCCCTCATAATTCCAGAGAAGGG  
CATTTCTGTCTTTTAAAGCACAGACTAAGGCTGGAACAGTCCATCCTTATCCCTCTTCTG  
GCTTGGGCCCTGACACCTAAGTCTTTCCACGGTTTATGTGTGTGCCTCATTCTTTCCC  
ACCAAGAATCCATCTTAGCGCCTCCTGCCAGCTGCCCTGGTGCTTTCTCCAAGGGCCATC  
AGTGTCTTGCTAGCTTGAGGGCTTAAGTCCTTATGCTGTGTAGTTTCGTTGTCAGAAC  
AAATTAATAATTTTCAGAGACGCTG

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GAGACCATGGCGAACGACTCTCCCGCGAAAAGTCTGGTGGACATCGACCTCTCCTCCCTG  
CGGGATCCTGCTGGGATTTTTGAGCTGGTGGAAAGTGGTTGGAAATGGCACCTATGGACAA  
GTCTATAAGGGTCGACATGTAAAAACGGGTCAGTTGGCAGCCATCAAAGTTATGGATGTC  
ACTGAGGATGAAGAGGAAGAAATCAAACCTGGAGATAAATATGCTAAAGAAATACTCTCAT  
CACAGAAACATTGCAACATATTATGGTGTCTTTCATCAAAAAGAGCCCTCCAGGACATGAT  
GACCAACTCTGGCTTGTTATGGAGTTCTGTGGGGCTGGGTCCATTACAGACCTTGTGAAG  
AACACCAAAGGGAACACACTCAAAGAAGACTGGATCGCTTACATCTCCAGAGAAATCCTG  
AGGGGACTGGCACATCTTCACATTCATCATGTGATTACCGGGATATCAAGGGCCAGAAT  
GTGTTGCTGACTGAGAATGCAGAGGTGAAACTTGTGACTTTGGTGTGAGTGCTCAGCTG  
GACAGGACTGTGGGGCGGAGAAATACGTTCATAGGCACTCCCTACTGGATGGCTCCTGAG  
GTCATCGCCTGTGATGAGAACCAGATGCCACCTATGATTACAGAAGTGATCTTTGGTCT  
TGTGGCATTACAGCCATTGAGATGGCAGAAGGTGCTCCCCCTCTCTGTGACATGCATCCA  
ATGAGAGCACTGTTTCTCATTCCCAGAAACCTCCTCCCCGGCTGAAGTCAAAAAAATGG  
TCGAAGAAGTTTTTTAGTTTTATAGAAGGGTGCCTGGTGAAGAATTACATGCAGCGGCCC  
TCTACAGAGCAGCTTTTGAACATCCTTTTATAAGGGATCAGCCAAATGAAAGGCAAGTT  
AGAATCCAGCTTAAGGATCATATAGATCGTACCAGGAAGAAGAGAGGCGAGAAAGATGAA  
ACTGAGTATGAGTACAGTGGGAGTGAGGAAGAAGAGGAGGAAGTGCTGAACAGGAAGGA  
GAGCCAAGTTCCATTGTGAACGTGCCTGGTGAAGTCTACTCTTCGCCGAGATTTCTGAGA  
CTGCAGCAGGAGAACAAGGAACGTTCCGAGGCTCTTCGGAGACAACAGTTACTACAGGAG  
CAACAGCTCCGGGAGCAGGAAGAATATAAAAGGCAACTGCTGGCAGAGAGACAGAAGCGG

**Fig. 9F**

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ATTGAGCAGCAGAAAGAACAGAGGCGACGGCTAGAAGAGCAACAAAGGAGAGAGCGGGAA  
GCTAGAAGGCAGCAGGAACGTGAACAGCGAAGGAGAGAACAAGAAGAAAAGAGGCGTCTA  
GAGGAGTTGGAGAGAAGGCGCAAAGAAGAAGAGGAGAGGAGACGGGCAGAAGAAGAAAAG  
AGGAGAGTTGAAAGAGAACAGGAGTATATCAGGCGACAGCTAGAAGAGGAGCAGCGGCAC  
TTGGAAGTCCTTCAGCAGCAGCTGCTCCAGGAGCAGGCCATGTTACTGGAGTGCCGATGG  
CGGGAGATGGAGGAGCACCGGCAGGCAGAGAGGCTCCAGAGGCAGTTGCAACAAGAACAA  
GCATATCTCCTGTCTCTACAGCATGACCATAGGAGGGCCGCACCCGCAGCACTCGCAGCAG  
CCGCCACCACCGCAGCAGGAAAGGAGCAAGCCAAGCTTCCATGCTCCCGAGCCCAAAGCC  
CACTACGAGCCTGCTGACCGAGCGCGAGAGGTGGAAGATAGATTTAGGAAAACCTAACAC  
AGCTCCCCTGAAGCCCAGTCTAAGCAGACAGGCAGAGTATTGGAGCCACCAGTGCCCTTC  
CGATCAGAGTCTTTTTCCAATGGCAACTCCGAGTCTGTGCATCCCGCCCTGCAGAGACCA  
GCGGAGCCACAGGTTCTGTGAGAACAACATCTCGCTCCCCTGTTCTGTCCCGTCGAGAT  
TCCCCACTGCAGGGCAGTGGGCAGCAGAATAGCCAGGCAGGACAGAGAACTCCACCAGT  
ATTGAGCCCAGGCTTCTGTGGGAGAGAGTGGAGAAGCTGGTGCCAGACCTGGCAGTGGC  
AGCTCCTCAGGGTCCAGCAACTCAGGATCCCAGCCCGGGTCTCACCTGGGTCTCAGAGT  
GGCTCCGGGGAACGCTTCAGAGTGAGATCATCATCAAAGTCTGAAGGCTCTCCATCTCAG  
CGCCTGGAAAATGCAGTGAAAAAACCTGAAGATAAAAAGGAAGTTTTTCAGACCCCTCAAG  
CCTGCTGATCTGACCGCACTGGCCAAAGAGCTTCGAGCAGTGGAAGATGTACGGCCACCT  
CACAAAGTAACGGACTACTCCTCATCCAGTGAGGAGTCGGGGACGACGGATGAGGAGGAC  
GACGATGTGGAGCAGGAAGGGGCTGACGAGTCCACCTCAGGACCAGAGGACACCAGAGCA  
GCGTCATCTCTGAATTTGAGCAATGGTGAAACGGAATCTGTGAAAACCATGATTGTCCAT  
GATGATGTAGAAAGTGAGCCGGCCATGACCCCATCCAAGGAGGGCACTCTAATCGTCCGC  
CGGACTCAGTCCGCTAGTAGCACACTCCAGAAACACAAATCTTCCTCCTCCTTTACACCT  
TTTATAGACCCCAGATTACTACAGATTTCTCCATCTAGCGGAACAACAGTGACATCTGTG  
GTGGGATTTTCCTGTGATGGGATGAGACCAGAAGCCATAAGGCAAGATCCTACCCGGAAA  
GGCTCAGTGGTCAATGTGAATCCTACCAACACTAGGCCACAGAGTGACACCCCGGAGATT  
CGTAAATACAAGAAGAGGTTTAACTCTGAGATTCTGTGTGCTGCCTTATGGGGAGTGAAT  
TTGCTAGTGGGTACAGAGAGTGGCCTGATGCTGCTGGACAGAAGTGGCCAAGGGAAGGTC  
TATCCTCTTATCAACCGAAGACGATTTCAACAAATGGACGTACTTGAGGGCTTGAATGTC  
TTGGTGACAATATCTGGCAAAAAGGATAAGTTACGTGTCTACTATTTGTCTGGTTAAGA  
AATAAAATACTTCACAAATGATCCAGAAGTTGAGAAGAAGCAGGGATGGACAACCGTAGGG  
GATTTGGAAGGATGTGTACATTATAAAGTTGTAAATATGAAAGAATCAAATTTCTGGTG  
ATTGCTTTGAAGAGTTCTGTGGAAGTCTATGCGTGGGCACCAAGCCATATCACAAATTT  
ATGGCCTTTAAGTCATTTGGAGAATTGGTACATAAGCCATTACTGGTGGATCTCACTGTT  
GAGGAAGGCCAGAGGTTGAAAGTGATCTATGGATCCTGTGCTGGATTCCATGCTGTTGAT  
GTGGATTCAAGATCAGTCTATGACATTTATCTACCAACACATATCCAGTGTAGCATCAAA  
CCCCATGCAATCATCATCCTCCCAATACAGATGGAATGGAGCTTCTGGTGTGCTATGAA  
GATGAGGGGGTTTATGTAAACACATATGGAAGGATCACCAAGGATGTAGTTCTACAGTGG

**Fig. 9G**

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GGAGAGATGCCTACATCAGTAGCATATATTCGATCCAATCAGACAATGGGCTGGGGAGAG  
AAGGCCATAGAGATCCGATCTGTGGAACCTGGTCACTTGGATGGTGTGTTTCATGCACAAA  
AGGGCTCAAAGACTAAAATTCTTGTGTGAACGCAATGACAAGGTGTTCTTTGCCTCTGTT  
CGGTCTGGTGGCAGCAGTCAGGTTTATTTTCATGACCTTAGGCAGGACTTCTCTTCTGAGC  
TGGTAGAAGCAGTGTGATCCAGGGATTACTGGCCTCCAGAGTCTTCAAGATCCTGAGAAC  
TTGGAATTCCTTGTAAC

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GCTTTCGGGGAGGTCTATGAGGGTCTGTCATGTCAAAACGGGCCAGCTTGCAGCCATCAAG  
GTTATGGATGTCACAGGGGATGAAGAGGAAGAAATCAAACAAGAAATTAACATGTTGAAG  
AAATATTCTCATCACCGGAATATTGCTACATACTATGGTGCTTTTATCAAAAAGAACCCA  
CCAGGCATGGATGACCAACTTTGGTTGGTGATGGAGTTTTGTGGTGCTGGCTCTGTACC  
GACCTGATCAAGAACACAAAAGGTAACACGTTGAAAGAGGAGTGGATTGCATACATCTGC  
AGGGAAATCTTACGGGGGCTGAGTCACCTGCACCAGCATAAAGTGATTTCGAGATATT  
AAAGGGCAAATGTCTTGCTGACTGAAATGCAGAAAGTTAACTAGTGGACTTTGGAGTC  
AGTGCTCAGCTTGATCGAACAGTGGGCAGGAGGAATACTTTCATTGGAACCTCCTACTGG  
ATGGCACCAGAAGTTATTGCCTGTGATGAAAACCCAGATGCCACATATGATTTCAAGAGT  
GACTTGTGGTCTTTGGGTATCACCGCCATTGAAATGGCAGAAGGTGCTCCCCCTCTCTGT  
GACATGCACCCCATGAGAGCTCTCTTCCTCATCCCCCGGAATCCAGCGCCTCGGCTGAAG  
TCTAAGAAGTGGTCAAAAAAATTCCAGTCATTTATTGAGAGCTGCTTGGTAAAGAATCAC  
AGCCAGCGACCAGCAACAGAACAAATTGATGAAGCATCCATTTATACGAGACCAACCTAAT  
GAGCGACAGGTCCGCATTCAACTCAAGGACCATATTGATAGAACAAGAAGAAGCGAGGA  
GAAAAAGATGAGACAGAGTATGAGTACAGTGGAAGTGAGGAAGAAGAGGAGGAGAATGAC  
TCAGGAGAGCCCAGCTCCATCCTGAATCTGCCAAGGGAGTCGACGCTGCGGAGGGACTTT  
CTGAGGCTGCAGCTGGCCAACAAGGAGCGTTCTGAGGCCCTACGGAGGCAGCAGCTGGAG  
CAGCAGCAGCGGGAGAATGAGGAGCACAAGCGGCAGCTGCTGGCCGAGCGTCAGAAGCGC  
ATCGAGGAGCAGAAAGAGCAGAGGGCGGCGGCTGGAGGAGCAACAAGGCGAGAGAAGGAG  
CTGCGGAAGCAGCAGGAGAGGGAGCAGCGCCGGCACTATGAGGAGCAGATGCGCCGGGAG  
GAGGAGAGGAGGCGTGCGGAGCATGAACAGGAATATAAGCGCAAACAATTGGAAGAACAG  
AGACAAGCAGAAAGACTGCAGAGGCAGCTAAAGCAAGAAAGAGACTACTTAGTTTCCCTT  
CAGCATCAGCGGCAGGAGCAGAGGCCTGTGGAGAAGAAGCCACTGTACCATTACAAAGAA  
GGAATGAGTCCTAGTGAGAAGCCAGCATGGGCCAAGGAGGTAGAAGAAGGTCAGGCTC  
AACCGGCAAAGTTCCCTGCCATGCCTCACAAGGTTGCCAACAGGATATCTGACCCCAAC  
CTGCCCCCAAGGTCGGAGTCCTTCAGCATTAGTGGAGTTCAGCCTGCTCGAACACCCCCC  
ATGCTCAGACCAGTCGATCCCCAGATCCCACATCTGGTAGCTGTAAATCCCAGGGACCT  
GCCTTGACCGCTCCAGTCAGTGCACGAGCAGCCCACAAAGGGCCTCTCTGGGTTTCAG  
GAGGCTCTGAACGTGACCTCCCACCGCGTGGAGATGCCACGCCAGAACTCAGATCCCACC  
TCGAAAATCCTCCTCTCCCCACTCGCATTGAAAAGTTTGACCGAAGCTCTTGGTTACGA

**Fig. 9H**

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CAGGAAGAAGACATTCCACCAAAGGTGCCTCAAAGAACAACCTTCTATATCCCCAGCATTA  
GCCAGAAAGAATTCTCCTGGGAATGGTAGTGCTCTGGGACCCAGACTAGGATCTCAACCC  
ATCAGAGCAAGCAACCCTGATCTCCGGAGAACTGAGCCCATCTTGGAGAGCCCCCTTGCG  
AGGACCAGCAGTGGCAGTTCCTCCAGCTCCAGCACCCCTAGCTCCCAGCCAGCTCCCAA  
GGAGGCTCCCAGCCTGGATCACAAGCAGGATCCAGTGAACGCACCAGAGTTCGAGCCAAC  
AGTAAGTCAGAAGGATCACCTGTGCTCCCCCATGAGCCTGCCAAGGTGAAACCAGAAGAA  
TCCAGGGACATTACCCGGCCCCAGTCGACCAGCTAGCTACAAAAAAGCTATAGATGAGGAT  
CTGACGGCATTAGCCAAAGAACTAAGAGAACTCCGGATTGAAGAAAACAAACCGCCCAATG  
AAGAAGGTGACTGATTACTCCTCCTCCAGTGAGGAGTCAGAAAGTAGCGAGGAAGAGGAG  
GAAGATGGAGAGAGCGAGACCCATGATGGGACAGTGGCTGTCAGCGACATACCCAGACTG  
ATACCAACAGGAGCTCCAGGCAGCAACGAGCAGTACAATGTGGGAATGGTGGGGACGCAT  
GGGCTGGAGACCTCTCATGCGGACAGTTTCAGCGGCAGTATTTCAAGAGAAGGAACCTTG  
ATGATTAGAGAGACGTCTGGAGAGAAGAAGCGATCTGGCCACAGTGACAGCAATGGCTTT  
GCTGGCCACATCAACCTCCCTGACCTGGTGCAGCAGAGCCATTCTCCAGCTGGAACCCCG  
ACTGAGGGACTGGGGCGCGTCTCAACCCATTCCCAGGAGATGGACTCTGGGACTGAATAT  
GGCATGGGGAGCAGCACCAAAGCCTCCTTCACCCCTTTGTGGACCCAGAGTATACCAG  
ACGTCTCCCACTGATGAAGATGAAGAGGATGAGGAATCATCAGCCGCAGCTCTGTTTACT  
GGCGAACTTCTTAGGCAAGAACAGGCCAACTCAATGAAGCAAGAAAGATTTCCGGTGGTA  
AATGTAAACCCAACCAACATTCCGGCCTCATAGCGACACACCAGAAATCAGAAAATACAAG  
AAACGATTCAACTCAGAAATACTTTGTGCAGCTCTGTGGGGTGTAACCTTCTGGTGGGG  
ACTGAAAATGGCCTGATGCTTTTGGACCGAAGTGGGCAAGGCAAAGTCTATAATCTGATC  
AACCGGAGGCGATTTCCAGCAGATGGATGTGCTAGAGGGACTGAATGTCCTTGTGACAATT  
TCAGGAAAGAAGAATAAGCTACGAGTTTACTATCTTTTCATGGTTAAGAAACAGAATACTA  
CATAATGACCCAGAAGTAGAAAAGAAACAAGGCTGGATCACTGTTGGGGACTTGGAAGGC  
TGTATACATTATAAAGTTGTTAAATATGAAAGGATCAAATTTTTTGGTGATTGCCTTAAAG  
AATGCTGTGGAAATATATGCTTGGGCTCCTAAACCGTATCATAAATTCATGGCATTTAAG  
TCTTTTGCAGATCTCCAGCACAAGCCTCTGCTAGTTGATCTCACGGTAGAAGAAGGTCAA  
AGATTAAAGGTTATTTTTGGTTCACACACTGGTTTCCATGTAATTGATGTTGATTCAGGA  
AACTCTTATGATATCTACACACCATCTCATATTCAGGGCAATATCACTCCTCATGCTATT  
GTCATCTTGCCTAAAACAGATGGAATGGAATGCTTGTGCTATGAGGATGAGGGGGTG  
TATGTAAACACCTATGGCCGGATAACTAAGGATGTGGTGCTCCAATGGGGAGAAATGCCC  
ACGTCTGTGGCCTACATTCATTCCAATCAGATAATGGGCTGGGGCGAGAAAGCTATTGAG  
ATCCGGTCAGTGGAACAGGACATTTGGATGGAGTATTTATGCATAAGCGAGCTCAAAGG  
TTAAAGTTTCTATGTGAAAGAAATGATAAGGTATTTTTTGCATCCGTGCGATCTGGAGGA  
AGTAGCCAAGTGTTTTTCATGACCCTCAACAGAAATTCATGAACTGGTAACAGAAG  
AGCACTTGGCACTTATCTTCATGGCGTTATTTCTAATTTAAAAGAACATAACTCATGTGG  
ACTTATGCCAGTCTAGAGGCAGAATCAGAAGGCTTGGTTGAACATATCGCTTTCCTTTT  
TCCTCTCCCTCCGCCCCCTCCAGTACAGTCCATCT

**Fig. 9 I**

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GCATTTGGGGAGGTGTATGAGGGTCGGCATGTCAAGACGGGGCAGCTGGCTGCCATCAAG  
GTCATGGATGTCACGGAGGACGAGGAGGAAGAGATCAAACAGGAGATCAACATGCTGAAA  
AAGTACTCTCACCACCGCAACATCGCCACCTACTACGGAGCCTTCATCAAGAAGAGCCCC  
CCGGGAAACGATGACCAGCTCTGGCTGGTGATGGAGTTCTGTGGTGCTGGTTCAGTGACT  
GACCTGGTAAAGAACACAAAAGGCAACGCCCTGAAGGAGGACTGTATCGCCTATATCTGC  
AGGGAGATCCTCAGGGGTCTGGCCCATCTCCATGCCCAAGGTGATCCATCGAGACATC  
AAGGGGCAGAATGTGCTGCTGACAGAGAATGCTGAGGTCAAGCTAGTGGATTTTGGGGTG  
AGTGCTCAGCTGGACCGCACCGTGGGCAGACGGAACACTTTCATTGGGACTCCCTACTGG  
ATGGCTCCAGAGGTCATCGCCTGTGATGAGAACCCTGATGCCACCTATGATTACAGGAGT  
GATATTTGGTCTCTAGGAATCACAGCCATCGAGATGGCAGAGGGAGCCCCCCTCTGTGT  
GACATGCACCCCATGCGAGCCCTCTTCCTCATTCCCTCGGAACCTCCGCCAGGGCTCAAG  
TCCAAGAAGTGGTCTAAGAAGTTCATTGACTTCATTGACACATGTCTCATCAAGACTTAC  
CTGAGCCGCCACCCACGGAGCAGCTACTGAAGTTTCCCTTCATCCGGGACCAGCCCACG  
GAGCGGCAGGTCCGCATCCAGCTTAAGGACCACATTGACCGATCCCGGAAGAAGCGGGGT  
GAGAAAGAGGAGACAGAATATGAGTACAGCGGCAGCGAGGAGGAAGATGACAGCCATGGA  
GAGGAAGGAGAGCCAAGCTCCATCATGAACGTGCCTGGAGAGTCGACTCTACGCCGGGAG  
TTTCTCCGGCTCCAGCAGGAAAATAAGAGCAACTCAGAGGCTTTAAACAGCAGCAGCAG  
CTGCAGCAGCAGCAGCAGCAGACCCCGAGGCACACATCAAACACCTGCTGCACCAGCGG  
CAGCGGCGCATAGAGGAGCAGAAGGAGGAGCGGCGCCGCGTGGAGGAGCAACAGCGGCGG  
GAGCGGGAGCAGCGGAAGCTGCAGGAGAAGGAGCAGCAGCGGCGGCTGGAGGACATGCAG  
GCTCTGCGGCGGGAGGAGGAGCGGCGGAGCGGAGCGGAGCAGGAATATATTCGTAC  
AGGCTAGAGGAGGAGCAGCGACAGCTCGAGATCCTTCAGCAACAGCTGCTCCAGGAACAG  
GCCCTGCTGCTGGAATACAAGCGGAAGCAGCTGGAGGAGCAGCGGCAGTCAGAACGTCTC  
CAGAGGCAGCTGCAGCAGGAGCATGCCTACCTCAAGTCCCTGCAGCAGCAGCAACAGCAG  
CAGCAGCTTCAGAAACAACAGCAGCAGCAGCTCCTGCCTGGGGACAGGAAGCCCCCTGTAC  
CATTATGGTCCGGGCATGAATCCCGCTGACAAACCAGCCTGGGCCCCGAGAGGTAGAAGAG  
AGAACAAGGATGAACAAGCAGCAGAACTCTCCCTTGGCCAAGAGCAAGCCAGGCAGCAG  
GGGCCTGAGCCCCCATCCCCAGGCCTCCCCAGGGCCCCCAGGACCCCTTTCCAGACT  
CCTCCTATGCAGAGGCCGGTGGAGCCCCAGGAGGGACCGCACAAAGAGCCTGGTGGCACAC  
CGGGTCCCACTGAAGCCATATGCAGCACCTGTACCCCGATCCCAGTCCCTGCAGGACCAG  
CCCACCCGAAACCTGGCTGCCTTCCCAGCCTCCCATGACCCCGACCCTGCCATCCCCGCA  
CCCACTGCCACGCCCAGTGCCCGAGGAGCTGTCATCCGCCAGAATTACAGACCCACCTCT  
GAAGGACCTGGCCCCAGCCCGAATCCCCAGCCTGGGTCCGCCAGATAACGAGGCCCA  
CCCAAGGTGCCTCAGAGGACCTCATCTATCGCCACTGCCCTTAACACCAGTGGGGCCGGA  
GGGTCCCGGCCAGCCAGGCAGTCCGTGCCAGACCTCGCAGCAACTCCGCCTGGCAAATC  
TATCTGCAAAGGCGGGCAGAGCGGGGACCCCCAAAGCCTCCAGGGCCCCCTGCTCAGCCC  
CCTGGCCCCGCCAACGCCTCTAGTAACCCCGACCTCAGGAGGAGCGACCCTGGCTGGGAA

**Fig. 9J**

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CGCTCGGACAGCGTCCTTCCAGCCTCTCACGGGCACCTCCCCAGGCTGGCTCACTGGAG  
CGGAACCGCGTGGGAGTCTCCTCCAAACCGGACAGCTCCCCTGTGCTCTCCCCTGGGAAT  
AAAGCCAAGCCCGACGACCACCGCTCACGGCCAGGCCGGCCCGCAGACTTTGTGTTGCTG  
AAAGAGCGGACTCTGGACGAGGCCCTCGGCCCTCCAAGAAGGCCATGGACTACTCGTCG  
TCCAGCGAGGAGGTGGAAAGCAGTGAGGACGACGAGGAGGAAGGCGAAGGCGGGCCAGCA  
GAGGGGAGCAGAGATACCCCTGGGGGCCGCGATGGGGATACAGACAGCGTCAGCACCATG  
GTGGTCCACGACGTCGAGGAGATCACCGGGACCCAGCCCCATACGGGGGCGGCACCATG  
GTGGTCCAGCGCACCCCTGAAGAGGAGCGGAACCTGCTGCATGCTGACAGCAATGGGTAC  
ACAAACCTGCCTGACGTGGTCCAGCCCAGCCACTCACCCACCGAGAACAGCAAAGGCCAA  
AGCCCACCCTCGAAGGATGGGAGTGGTGA CTACCAGTCTCGTGGGCTGGTAAAGGCCCT  
GGCAAGAGCTCGTTCACGATGTTTGTGGATCTAGGGATCTACCAGCCTGGAGGCAGTGGG  
GACAGCATCCCCATCACAGCCCTAGTGGGTGGAGAGGGCACTCGGCTCGACCAGCTGCAG  
TACGACGTGAGGAAGGGTTCTGTGGTCAACGTGAATCCCACCAACACCCGGGGCCACAGT  
GAGACCCCTGAGATCCGGAAGTACAAGAAGCGATTCAACTCCGAGATCCTCTGTGCAGCC  
CTTTGGGGGGTCAACCTGCTGGTGGGCACGGAGAACGGGCTGATGTTGCTGGACCGAAGT  
GGGCAGGGCAAGGTGTATGGACTCATTGGGCGGCGACGCTTCCAGCAGATGGATGTGCTG  
GAGGGGCTCAACCTGCTCATCACCATCTCAGGGAAAAGGAACAACTGCGGGGTGTATTAC  
TTGTCCTGGCTCCGGAACAAGATTCTGCACAATGACCCAGAAGTGGAGAAGAAGCAGGGC  
TGGACCACCGTGGGGGACATGGAGGGCTGCGGGCACTACCGTGTTGTGAAATACGAGCGG  
ATTAAGTTCTGGTCATCGCCCTCAAGAGCTCCGTGGAGGTGTATGCCTGGGCCCCCAA  
CCCTACCACAAATTTCATGGCCTTCAAGTCCTTTGCCGACCTCCCCACCGCCCTCTGCTG  
GTGACCTGACAGTAGAGGAGGGGCAGCGGCTCAAGGTCATCTATGGCTCCAGTGCTGGC  
TTCCATGCTGTGGATGTGACTCGGGGAACAGCTATGACATCTACATCCCTGTGCACATC  
CAGAGCCAGATCACGCCCCATGCCATCATCTTCTCCCCAACACCGACGGCATGGAGATG  
CTGCTGTGCTACGAGGACGAGGGTGTCTACGTCAACACGTACGGGCGCATCATTAAGGAT  
GTGGTGTGCTGCAGTGGGGGAGATGCCTACTTCTGTGGCCTACATCTGCTCCAACCAGATA  
ATGGGCTGGGGTGAGAAAGCCATTGAGATCCGCTCTGTGGAGACGGGCCACCTCGACGGG  
GTCTTCATGCACAAACGAGCTCAGAGGCTCAAGTTCCTGTGTGAGCGGAATGACAAGGTG  
TTTTTTGCCTCAGTCCGCTCTGGGGGCAGCAGCCAAGTTTACTTCATGACTCTGAACCGT  
AACCGCATCATGAACTGGTGACGGGGCCCTGGGCTGGGGCTGTCCCACACTGGACCCAGC  
TCTCCCCCTGCAGCCAGGCTTCCCGGGGCGCCCCCTCTTCCCCCTCCCTGGGCTTTTGCTT  
TACTGGTTTGATTTCACTGGAGCCTGCTGGGAACGTGACCTCTGACCCCTGA

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CAATGTAAACCACTCTATGTCTCTCCTGCATGTAAAAAACCACTAATCCACATGTATGA  
AAAGGAGTTCACTTCTGAGATCTGCTGTGGTTCTTTGTGGGGAGTCAATTTGCTGTTGGG  
AACCCGATCTAATCTATATCTGATGGACAGAAGTGAAAGGCTGACATTACTAACTTAT  
AAGGCGAAGACCATTCCGCCAGATTCAAGTCTTAGAGCCACTCAATTTGCTGATTACCAT

**Fig. 9K**  
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CTCAGGTCATAAGAACAGACTTCGGGTGTATCATCTGACCTGGTTGAGGAACAAGATTTT  
GAATAATGATCCAGAAAGTAAAAGAAGGCAAGAAGAAATGCTGAAGACAGAGGAAGCCTG  
CAAAGCTATTGATAAGTTAACAGGCTGTGAACACTTCAGTGTCCTCCAACATGAAGAAAC  
AACATATATTGCAATTGCTTTGAAATCATCAATTCACCTTTATGCATGGGCACCAAAGTC  
CTTTGATGAAAGCACTGCTATTAAAGTATTTCCAACACTTGATCATAAGCCAGTGACAGT  
TGACCTGGCTATTGGTTCTGAAAAAAGACTAAAGATTTTCTTCAGCTCAGCAGATGGATA  
TCACCTCATCGATGCAGAATCTGAGGTTATGTCTGATGTGACCCTGCCAAAGAATCCCCT  
GGAAATCATTATACCACAGAATATCATCATTTTACCTGATTGCTTGGGAATTGGCATGAT  
GCTCACCTTCAATGCTGAAGCCCTCTCTGTGGAAGCAAATGAACAACTCTTCAAGAAGAT  
CCTTGAAATGTGGAAAGACATACCATCTTCTATAGCTTTTGAATGTACACAGCGAACCAC  
AGGATGGGGCCAAAAGGCCATTGAAGTGCGCTCTTTGCAATCCAGGGTTCTGGAAAGTGA  
GCTGAAGCGCAGGTCAATTAAGAAGCTGAGATTCTGTGCACCCGGGGTGACAAGCTGTT  
CTTTACCTCTACCCTGCGCAATCACCACAGCCGGGTTTACTTCATGACACTTGGAAAAC  
TGAAGAGCTCCAAAGCAATTATGATGTCTAAAAGTTTCCAGTGATTTATTACCACATTAT  
AAACATCATGTATAGGCAGTCTGCATCTTCAGATTTTCAAGATTAATGAGTATTCAGTT  
TTATTTTTAGTAAAGATTAAATCCAAAACCTTTACTTTTAAATGTAGCACAGAATAGTTT  
ATGAGAAATGCAGCTTTATGTATAAAATTAAGTATAGCAAGCTCTAGGTACTCCAATGGT  
GTACAATGTCTTTTGCACAACTTTTGTAACTTTTGTACTGTGAATTCAAACATTACTCT  
TTGGACAGTTTGGACAGTATCTGTATTTCAGATTTTACAACATGGAGTAAAGAAACCTGTT  
ATGAATTAGATTACAAGCAGCCTTCAAAGAATTGGCACTGGGATAAGATTTTTTCAGAAA  
AGAAAAACATCGGCAAACT

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CCGCCATGAACCCCGGCTTCGATTTGTCCCGCCGGAACCCGCAGGAGGACTTCGAGCTGA  
TTCAGCGCATCGGCAGCGGCACCTACGGCGACGTCTACAAGGCACGGAATGTTAACTG  
GTGAATTAGCAGCAATTAAAGTAATAAAATTGGAACCAGGAGAAGACTTTGCAGTTGTGC  
AGCAAGAAATTATTATGATGAAAGACTGTAAACACCCAAATATTGTTGCTTATTTTGGAA  
GCTATCTCAGGCGAGATAAGCTTTGGATTTGCATGGAGTTTTGTGGAGGTGGTTCTTTAC  
AGGATATTTATCACGTAAGTGGACCTCTGTGCAAGTCAAATTGCATATGTTAGCAGAG  
AAACACTGCAGGGATTATATTATCTTCACAGTAAAGGAAAAATGCACAGAGATATAAAGG  
GAGCTAACATTCTATTAACGGATAATGGTCATGTGAAATTGGCTGATTTTGGAGTATCTG  
CACAGATAACAGCTACAATTGCCAAACGGAAGTCTTTCATTGGCACACCATATTGGATGG  
CTCCAGAAGTTGCAGCTGTTGAGAGGAAGGGGGTTACAATCAACTCTGTGATCTCTGGG  
CAGTGGGAATCACTGCCATAGAACTTGACAGAGCTTCAGCCTCCTATGTTTGACTTACACC  
CAATGAGAGCATTATTTCTAATGACAAAAAGCAATTTTCAGCCTCCTAACTAAAGGATA  
AAATGAAATGGTCAAATAGTTTTCATCACTTTGTGAAAATGGCACTTACCAAAAATCCGA  
AAAAAAGACCTACTGCTGAAAAATTATTACAGCATCCTTTTGTAAACACAACATTTGACAC  
GGTCTTTGGCAATCGAGCTGTTGGATAAAGTAAATAATCCAGATCATTCCACTTACCATG

**Fig. 9L**

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ATTTGATGATGATGATCCTGAGCCTCTTGTTGCTGTACCACATAGAATTCACTCAACAA  
GTAGAAACGTGAGAGAAGAAAAACACGCTCAGAGATAACCTTTGGCCAAGTGAAATTTG  
ATCCACCCTTAAGAAAGGAGACAGAACCACATCATGAACTTCCCGACAGTGATGGTTTTT  
TGGACAGTTCAGAAGAAATATACTACACTGCAAGATCTAATCTGGATCTGCAACTGGAAT  
ATGGACAAGGACACCAAGGTGGTTACTTTTTAGGTGCAAACAAGAGTCTTCTCAAGTCTG  
TTGAAGAAGAATTGCATCAGCGAGGACACGTCGCACATTTAGAAGATGATGAAGGAGATG  
ATGATGAATCTAAACACTCAACTCTGAAAGCAAAAATTCCACCTCCTTTGCCACCAAAGC  
CTAAGTCTATCTTCATACCACAGGAAATGCATTCTACTGAGGATGAAAATCAAGGAACAA  
TCAAGAGATGTCCCATGTCAGGGAGCCAGCAAAGCCATCCCAAGTTCCACCTAGACCAC  
CACCTCCAGATTACCCCCACACAAACCTGTTGCCTTAGGAAATGGAATGAGCTCCTTCC  
AGTTAAATGGTGAACGAGATGGCTCATTATGTCAACAACAGAATGAACATAGAGGCACAA  
ACCTTTCAAGAAAAGAAAAGAAAGATGTACCAAAGCCTATTAGTAATGGTCTTCCTCCAA  
CACCTAAAGTGCATATGGGTGCATGTTTTTCAAAGTTTTTAATGGGTGTCCCTTGAAAA  
TTCCTGTGCATCATCATGGATAAACCCAGATACAAGAGATCAGTACTTGATATTTGGTG  
CCGAAGAAGGGATTTATACCTCAATCTTAATGAACTTCATGAAACATCAATGGAACAGC  
TATTCCTCGAAGGTGTACATGGTTGTATGTAATGAACAATTGCTTGCTATCAATATCTG  
GTAAAGCTTCTCAGCTTTATTCCCATAATTTACCAGGGCTTTTTGATTATGCAAGACAAA  
TGCAAAAGTTACCTGTTGCTATTCCAGCACACAACTCCCTGACAGAATACTGCCAAGGA  
AATTTTCTGTATCAGCAAAAATCCCTGAAACCAAATGGTGCCAGAAGTGTTGTGTTGTAA  
GAAATCCTTACACGGGCCATAAATACCTATGTGGAGCACTTCAGACTAGCATTGTTCTAT  
TAGAATGGGTTGAACCAATGCAGAAATTTATGTTAATTAAGCACATAGATTTTCTTATAC  
CATGTCCACTTAGAATGTTTGAAATGCTGGTAGTTCCTGAACAGGAGTACCCTTTAGTTT  
GTGTTGGTGTGAGTAGAGGTAGAGACTTCAACCAAGTGGTTCGATTTGAGACGGTCAATC  
CAAATTCTACCTCTTCATGGTTTACAGAATCAGATACCCACAGACAAATGTTACTCATG  
TAACCCAACTGGAGAGAGATACCATCCTTGATGCTTGGACTGTTGTATAAAAATAGTAA  
ATCTCCAAGGAAGATTAAAATCTAGCAGGAAATTGTCATCAGAACTCACCTTTGATTTC  
AGATTGAATCAATAGTGTGCCTACAAGACAGTGTGCTAGCTTTCTGGAAACATGGAATGC  
AAGGTAGAAGTTTTAGATCTAATGAGGTAACACAAGAAATTTAGATAGCACAGAATTT  
TCAGGCTGCTTGGATCTGACAGGGTCGTGGTTTTGGAAAGTAGGCCAACTGATAACCCCA  
CAGCAAAATAGCAATTTGTACATCCTGGCGGGTCATGAAAACAGTTACTGAGAATTGTTGT  
GCTTTGACAGTTAACTCTAGAAAGAAAGAACTACCACTGCAACATTAATGGATGCTTG  
AAGCTGTACAAAAGCTGCAGTAACCTGTCTTCAGTTACTTTGTAATTTATTGTGGCATGA  
GATAAGATGGGGAAAATTTTGTGTTTAAAGTGGTATGGATATATTTAGCATATTGAACCACA  
CAAGTGCTTAATTCATTGTTATGTAATCTTTGTACATATAGGCAGTATTTTTTCTGTGAA  
ACTTCATATTGCTGAAGACATACACTAAGAATTTATGTAGATAATGTACTTTTATGAGAT  
GTACAAGTAAGTGTCTTATCTGTACAGATGTAAATGTTGATGAAAATGCAATTGGGGTTA  
ATATTTTAAGAATTTCTTAGTATATTCTTGGGTGTGGCTATATTACAAAATGGGATGCTG  
GCAATGAAACAATACATTTAACACTATTGTATTTTTATTATATGTAATTTAGTAATATGA

**Fig. 9M**

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ATATAAATCTTGTAACCTTTTAAAATTGTAATGGAGGCTGTAATCATTTTATAATCTTTTT  
AATTTTAATGCAAGTACACTGGTGTATATTTGCACAAAGTATTGATATGTGATGTATT  
AAGTCACAAAAGTAAGCTGTGACATTGTCTATAAGCATTGGCTCCACAAATGTATTGG  
ATTGTTTTCTATGTGAAGCAAACCAATTATAATTAACCACATGTTGTAGTAACTGGTCTT  
TTTATATTTAAGCAGAATCCTGTAAGATTGCTTGTCTTTGCTTAAAAACAATACCTTTGA  
ACATTTTTGAATCACAGAATAGCGGTACCATGATAGAATACTGCAATTGTGGTCAGAATT  
ACAGTATGCACAAAGAATTAATTAGCATTATTAAGAGTCCTCACTAAACATTTTATATG  
ATCACACTGAAGAACTGTAACATTCCATAGAGTGAAGTGGTTCAAATTTCTCTTGAATT  
TTTACTTTTGTGGCCTTATTTTATGATCCTTTTTCATATTTCTTTTGACTTAGAGTATTA  
ATACATGGCCAAAATAATTTAGTTACTACCTCATACAAACAATATAATGGTTACTACACA  
TCACAGGAACTTAGTTTTGGTTAAGTCATTTTTGATTGCTTTTTTCCAATGGAATATGT  
ATATACCAGGTTTTAGCAAATGCACACTTTTGGCTCTTTTTGGTATATGTTCTTTATAT  
TTAATGTGAGTATATACACTAAGAACAACCTAAATTGTGATTTATGATCTTCATTTATT  
TTAATGATAATGGTTTTAAAATATGTTCTGATTGTACATATTGTAAAATAAACATGTTT  
TTT

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GGGAGGGTCCTTGTGGCGCCGGGCGGGGTCCTGCGTGGAGAGTGGGACGCAACGCCG  
AGACCGCGAGCAGAGGCTGCGCACAGCCGGATCCGGCACTCAGCGACCGGACCCAAGGAT  
CCGCCGGGGAACAAGCCACAGGAGAGCGACTCAGGAACAAGTGTGGGAGAGGAAGCGGCG  
GCGGCGGCGCCGGGCCCCGGGGTGGTGACAGCAGGTCTGAGGTTGCATCATAAATACAAA  
GGACTGAAGTTATAAAAGAGAAAAAGAGAAGTTTGCTGCTAAATGAATCTGAGCAATATG  
GAATATTTTGTGCCACACACAAAAAGGTACTGAAGATTTACCCCCAAAAAAATTTGTCA  
ATGAGAAATAAAGCTAACTGATATCAAAAAGCAGAGCCTGCTCTACTGGCCATCATGCGT  
AAAGGGGTGCTGAAGGACCCAGAGATTGACGATCTATTCTACAAAGATGATCCTGAGGAA  
CTTTTTATTGGTTTGCATGAAATTGGACATGGAAGTTTTGGAGCAGTTTATTTTGCTACA  
AATGCTCACACCAATGAGGTGGTGGCAATTAAGAAGATGTCCTATAGTGGGAAGCAGACC  
CATGAGAAATGGCAAGATATTCTTAAGGAAGTTAAATTTTACGACAATTGAAGCATCCT  
AATACTATTGAGTACAAAGGCTGTTACTTGAAAGAACACACTGCTTGGTTGGTGTATGGA  
TATTGCTTAGGCTCAGCCTCTGATTTATTAGAAGTTCATAAAAAACCACTTCAGGAAGTG  
GAGATCGCTGCCATTACTCATGGAGCCTTGCATGGACTAGCCTACCTACATTCTCATGCA  
TTGATTCATAGGGATATTAAAGCAGGAAATATTCTTCTAACAGAGCCAGGTCAGGTAAAA  
CTAGCTGATTTTGGATCTGCTTCAATGGCTTCTCCTGCCAACTCCTTCGTGGGCACACCT  
TACTGGATGGCTCCAGAGGTGATCTTAGCTATGGATGAAGGACAGTATGATGGGAAAGTT  
GATATTTGGTCACTTGGCATCACTTGATTGAATTGGCGGAACGGAAGCCGCCCTTTTC  
AACATGAATGCAATGAGTGCCTTATATCACATTGCCCAGAATGACTCCCCAACGTTACAG  
TCTAATGAATGGACAGACTCCTTTAGGAGATTTGTTGATTACTGCTTGCAGAAAATACCT  
CAGGAAAGGCCAACATCAGCAGAACTATTAAGGCATGACTTTGTTGACGAGACCGGCCA

**Fig. 9N**

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CTACGTGTCCTCATTGACCTCATAACAGAGGACAAAAGATGCAGTTCGTGAGCTAGATAAC  
CTACAGTACCGAAAAATGAAAAAATACTTTTCCAAGAGACACGGAATGGACCCTTGAAT  
GAGTCACAGGAGGATGAGGAAGACAGTGAACATGGAACCAGCCTGAACAGGGAAATGGAC  
AGCCTGGGCAGCAACCATTTCCATTCCAAGCATGTCCGTGAGCACAGGCAGCCAGAGCAGC  
AGTGTGAACAGCATGCAGGAAGTCATGGACGAGAGCAGTTCCGAACTTGTCATGATGCAC  
GATGACGAAAGCACAATCAATTCCAGCTCCTCCGTGCGTGCATAAGAAAGATCATGTATTC  
ACAAGGGATGAGGCGGGCCACGGCGATCCCAGGCCTGAGCCGCGGCCTACCCAGTCAGTT  
CAGAGCCAGGCCCTCCACTACCGGAACAGAGAGCGCTTTGCCACGATCAATCAGCATCT  
TTGGTTACACGACAGATCCATGAGCATGAGCAGGAGAACGAGTTGCGGGAACAGATGTCA  
GGTTATAAGCGGATGCGGCGCCAGCACCAGAAGCAGCTGATCGCCCTGGAGAACAAGCTG  
AAGGCTGAGATGGACGAGCACCGCCTCAAGCTACAGAAGGAGGTGGAGACGCATGCCAAC  
AACTCGTCCATCGAGCTGGAGAAGCTGGCCAAGAAGCAAGTGGCTATCATAGAAAAGGAG  
GCAAAGGTAGCTGCAGCAGATGAGAAGAAGTTCCAGCAACAGATCTTGGCCCAGCAGAAG  
AAAGATTTGACAACTTTCTTAGAAAGTCAGAAGAAGCAGTATAAGATTTGTAAGGAAAA  
ATAAAAGAGGAAATGAATGAGGACCATAGCACACCCAAGAAAGAGAAGCAAGAGCGGATC  
TCCAAACATAAAGAGAACTTGCAGCACACACAGGCTGAAGAGGAAGCCCACCTTCTCACT  
CAACAGAGACTGTACTACGACAAAAATTGTCGTTTCTTCAAGCGGAAAATAATGATCAAG  
CGGCACGAGGTGGAGCAGCAGAACATTCGGGAGGAACTAAATAAAAAGAGGACCCAGAAG  
GAGATGGAGCATGCCATGCTAATCCGGCAGCAGAGTCCACCCGAGAGCTAGAGTACAGG  
CAGCTGCACACGTTACAGAAGCTACGCATGGATCTGATCCGTTTACAGCACCAGACGGAA  
CTGGAAAACCAGCTGGAGTACAATAAGAGGCGAGAAAGAGAAGTGCACAGAAAGCATGTC  
ATGGGACTTCGGCAACAGCCAAAAAACTTAAAGGCCATGGAAATGCAATTAAAAAACAG  
TTTCAGGACACTTGCAAAGTACAGACCAAACAGTATAAAGCACTCAAGAATCACCAGTTG  
GAAGTTACTCCAAAGAATGAGCACAAAACAATCTTAAAGACACTGAAAGATGAGCAGACA  
AGAAAACCTTGCCATTTTGGCAGAGCAGTATGAACAGAGTATAAATGAAATGATGGCCTCT  
CAAGCGTTACGGCTAGATGAGGCTCAAGAAGCAGAATGCCAGGCCTTGAGGCTACAGCTC  
CAGCAGGAAATGGAGCTGCTCAACGCCTACCAGAGCAAAATCAAGATGCAAACAGAGGCA  
CAACATGAACGTGAGCTCCAGAAGCTAGAGCAGAGAGTGTCTCTGCGCAGAGCACACCTT  
GAGCAGAAGATTGAAGAGGAGCTGGCTGCCCTTCAGAAGGAACGCAGCGAGAGAATAAAG  
AACCTATTGGAAAGGCAAGAGCGAGAGATTGAAACTTTTGACATGGAGAGCCTCAGAATG  
GGATTTGGGAATTTGGTTACATTAGATTTTCTAAGGAGGACTACAGATGAGATTAAATT  
TTTTGCCATTTACAAAAAAGAAAAAAGAAAAACAGAAAAAATTACAGACCTTGCAA  
AACCACATTCCTCATTTTAAACGGGCGTTGCTCTCACTCTCTCTCTCTTACTCTTACTG  
ACATCGTGTGCGACTAGTGCCTGTTTATTCTTACTCCATCAGGGGCCCCCTTCTCCCCC  
CGTGTCAACTTTAGTGCTGGCCAAAACCTGGCCGTCTTCTATTACAGTACACGTCA  
CAGTATTGATGTGATTCAAAATGTTTCAGTGAAAACCTTTGGAGACAGTTTTAACAAAACC  
AATAAACCAACAACAAAAAAGTGGATGTATATTGCTTTAAGCAATCACTCATTACCACC  
AATCTGTGAAAGTAAAGCAAAAAATAATAATAATAATGCCAAGGGGGAGAGAGACACAA

**Fig. 9 O**

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TATCCGCAGCCTTACACCTTAACTAGCTGCTGCATTATTTTATTTTATTTTATTTTATTTTGTG  
GTAATTTATTCATCAGGAATAAAAAAACAAAGTTTTATTAAAGATTGAAAATTTGATACA  
TTTTACAGAACTAATTGTGATGTACATATCAGTGGTGACATATTATTACTTTTTTTGGGG  
ACGGGGGGGTGGGTGGGGTGAAGAGATCTTGTGATTTTTTAAGAACCTGCTGGCAAGAGTT  
AACTTGCTTCAGCATATTCTGATTGTATCATAATCATTTTCTGCTGTTGCAGAGGATGT  
GAATACACTTAAGGAGCTCACAGAATCCCAGTAGCACAAATTGGGCTTTGGCAAATCGTG  
TATTTTGTGTATAGAAGGAATTTAAGGAGAGGTATTACTTATTTTCATATTGTATTTAA  
CTGTTTCTCTGATCAAATTTTTTTACTTCCTCCTCCTGTTCTCCTCCACCTCCCTCCTTT  
TCCAGTTCAGTATTTGGAGTTCAACACTGTCTCTCAATCAGATCATCTTGATCTTTTTCT  
TTATCTCCCTTCCCCTTCCCTAAGTCCCATTTCTTGGTCATAAATATTGCATTATTCACAC  
TTTCAAACCTGTGTATTTTCTTACAATAAAAAATGATGAAAAAAAAAAAAAAAAAAAAA

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TATTGAATTGGCGGAACGGAAGCCTCCTTTATTTAATATGAATGCAATGAGTGCCTTATA  
TCACATAGCCCAAAATGAATCCCCTACACTACAGTCTAATGAATGGTCTGATTATTTTCG  
CAACTTTGTAGATTCTTGCCTCCAGAAAATCCCTCAAGATCGACCTACATCAGAGGAACT  
TTTAAAGCACATATTTGTTCTTCGGGAGCGCCCTGAAACCGTGTTAATAGATCTCATTCA  
GAGGACAAAGGATGCAGTAAGAGAGCTGGACAATCTGCAGTATCGAAAGATGAAGAACT  
CCTTTTCCAGGAGGCACATAATGGACCAGCAGTAGAAGCACAGGAAGAAGAAGAGGAACA  
AGATCATGGTGTGGCCGGACAGGAACAGTTAATAGTGTGGAAGTAATCAATCCATTCC  
CAGCATGTCCATCAGTGCCAGCAGCCAAAGCAGTAGTGTAAACAGTCTTCCAGATGTCTC  
AGATGACAAGAGTGAGCTAGACATGATGGAGGGAGACCACACAGTGATGTCTAACAGTTC  
TGTTATCCATTTAAAACAGAGGAAGAAAATTACAGAGAAGAGGGAGATCCTAGAACAAG  
AGCATCAGATCCACAATCTCCACCCCAAGTATCTCGTCACAAATCACACTATCGTAATCG  
AGAACACTTTGCTACTATACGGACAGCATCACTGGTTACGAGGCAAATGCAAGAACATGA  
GCAGGACTCTGAGCTTAGAGAACAAATGTCTGGCTATAAGCGAATGAGGCGACAACATCA  
AAAGCAACTGATGACTCTGGAAAAAAGCTAAAGGCTGAGATGGATGAACATCGCCTCAG  
ATTAGACAAAGATCTTGAAACTCAGCGTAACAATTTTGCTGCAGAAATGGAGAACTTAT  
CAAGAAACACCAGGCTGCCATGGAGAAAGAGGCTAAAGTGATGTCCAATGAAGAGAAAAA  
ATTTTCAGCAACATATTCAGGCCCAACAGAAGAAAGAACTGAATAGTTTTCTCGAGTCCCA  
GAAAAGAGAGTATAAACTTCGAAAAGAGCAGCTTAAAGAGGAGCTAAATGAAAACCAGAG  
TACCCCCAAAAAAGAAAAACAGGAGTGGCTTTCAAAGCAGAAGGAGAATATACAGCATTT  
CCAAGCAGAAGAAGAAGCTAACCTTCTTCGACGTCAAAGACAATACCTAGAGCTGGAATG  
CCGTGCTTCAAGAGAAGAATGTTACTTGGGCGTCATAACTTAGAGCAGGACCTTGTCAG  
GGAGGAGTTAAACAAAAGACAGACTCAGAAGGACTTAGAGCATGCCATGCTACTCCGACA  
GCATGAATCTATGCAAGAACTGGAGTTCGCCACCTCAACACAATTCAGAAGATGCGCTG  
TGAGTTGATCAGATTACAGCATCAAACCTGAGCTCACTAACCAGCTGGAATATAATAAGCG  
AAGAGAACGAGAAGCTAAGACGAAAGCATGTCATGGAAGTTCGACAACAGCCTAAGAGTTT

**Fig. 9P**  
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GAAGTCTAAAGAACTCCAAATAAAAAAGCAGTTTCAGGATAGCTGCAAAATCCAAACCAG  
ACAGTACAAAGCATTAAGAAATCACCTGCTGGAGACTACACCAAAGAGTGAGCACAAGC  
TGTTCTGAAACGGCTCAAGGAGGAACAGACCCGGAAATTAGCTATCTTGGCTGAGCAGTA  
TGATCACAGCATTAAATGAAATGCTCTCCACACAAGCCCTGCGTTTGGATGAAGCACAGGA  
AGCAGAGTGCCAGGTTTTGAAGATGCAGCTGCAGCAGGAACTGGAGCTGTTGAATGCGTA  
TCAGAGCAAAATCAAGATGCAAGCTGAGGCACAACATGATCGAGAGCTTCGCGAGCTTGA  
ACAGAGGGTCTCCCTCCGGAGGGCACTCTTAGAACAAAAGATTGAAGAAGAGATGTTGGC  
TTTGCAGAAATGAGCGCACAGAACGAATACGAAGCCTGTTGGAACGTCAAGCCAGAGAGAT  
TGAAGCTTTTGA CTCTGAAAGCATGAGACTAGGTTTTAGTAATATGGTCCTTTCTAATCT  
CTCCCCTGAGGCATTTCAGCCACAGCTACCCGGGAGCTTCTGGTTGGTCACACAACCCTAC  
TGGGGGTCCAGGACCTCACTGGGGTCATCCCATGGGTGGCCCAACCACAAGCTTGGGGCCA  
TCCAATGCAAGGTGGACCCAGCCATGGGGTCACCCTTCAGGGCCAATGCAAGGGGTACC  
TCGAGGTAGCAGTATGGGAGTCCGCAATAGCCCCAGGCTCTGAGGCGGACAGCTTCTGG  
GGGACGGACGGAGCAGGGCATGAGCAGAAGCACGAGTGTCACTTCACAAATATCCAATGG  
GTCACACATGTCTTATACATAACTTAATAATTGAGAGTGGCAATTCCGCTGGAGCTGTCT  
GCCAAAAGAACTGCCTACAGACATCATCACAGCAGCCTCCTCACTTGGGTACTACAGTG  
TGGAAGCTGAGTGCATATGGTATATTTTATTCATTTTTGTAAAGCGTTCTGTTTTGTGTT  
TACTAATTGGGATGTCATAGTACTTGGCTGCCGGGTTTGTGTTTTTGGGGAAATTTTG  
AAAAGTGGAGTTGATATTAATAAATAAATGTGTATGTGTGTACATATATATACACACACAT  
ACACATATATTATGCATGTGGTGAAAAGAATTGGCTAGATAGGGGATTTTTCTGAACACT  
GCAAAAATAGAACGTAGCAAAATGGCTTCAGTTATCACTTTTGGGTGTCTGTATCCTAAG  
AAGTTTCTGAAAAGATCTAAAGCCTTTTTATCCCATATCCCAAATTCTTATGAGCCACTC  
ACAGCAGGCAGCATATGTTGAAATAAGTTATTACTGGTACACACCTGCATTGCCTCACCA  
GTGTATTTATTTGTTATTAATTTGATCTGACTTCTCAGCCTCATTTGGACTAAAAAAGA  
AAGCAGAAATCCATGAACACATTGCTTCTCGGCCTTTTGGCTAAGATCAAGTGTAGAAAT  
CCATGAACACTAAAGGACTTCATTGATTTTTTCAGAGAGTAGAAAACAACCTTAGTTTTTC  
TTTTTCTCTGAATGCGTCATAGGCTTGTGAGTGATTTTTGTCCATTCAATTGTGCCTTCT  
TTGTATTATGATAAGATGGGGTACTTAAGGAGATCACAAGTTGTGTGAGGATTGCATTA  
ACAAACCTATGAGCCTTCAATGGGGAAGACCAGAAGGGTGAGAGGGGCCCTGAAAGTTCA  
TATGGTGGGTATGTCCCGCAGCAGAGTGAGGAGATGAAGCTTACGTGTCCTGACGTTTTG  
TTGCTTATACTGTGATATCTCATCCTAGCTAAGCTCTATAATGCCCAAGACCCCAAACAG  
TACTTTTACTTTGTTTGTACAAAACAAAGACATATAGCCAATACAAATCAAATGCCGGA  
GGTGTTTGATGCCATATTTGCAAATTGCCATCTATTGAAATTCTCGTCACACTACATAGA  
CATAATTGTTATCTCCTTTTGGCTTATGTGATTTTCTGTTTACAAGTAGAATAGCCAATT  
ATTTAAATGTTTAGTTGCCACAGTGAACCAGGAGTCACTGAGCCAATGACTTTACCAGCT  
GCTGACTAATCTTCATCACCCTGTAGATTTTGTGTCATGTGCAGGTCCTCTATTTTTAA  
TTGCTGTTTTCGTTGCTGCAGTACTTTACAACTTCTAGTTCGTTGAGACTTAGTGACCA  
TTTGGCATCAAGTTAACATCACACAATAGGAAACACCACTTCCACAAGTCTCAAGCCTCA

**Fig. 9Q**

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GTGCTAAAGTACTACTGAAAAGGAACTAGGAAGTTTGGCCAATT

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GCAGGATGCCATCAACTAACAGAGCAGGCAGTCTAAAGGACCCTGAAATTGCAGAGCTCT  
TCTTCAAAGAAGATCCGGAAAAGCTCTTCACAGATCTCAGAGAAATCGGCCATGGGAGCT  
TTGGAGCAGTATATTTTGCACGAGATGTGCGTACTAATGAAGTGGTGGCCATCAAGAAAA  
TGTCTTATAGTGGAAGCAGTCTACTGAGAAATGGCAGGATATTATTAAGGAAGTCAAGT  
TTCTACAAAGAATAAAACATCCCAACAGTATAGAATACAAAGGCTGCTATTTACGTGAAC  
ACACAGCATGGCTTGTAATGGAATATTGTTTAGGATCTGCTTCAGATTTATTAGAAGTTC  
ATAAAAAGCCATTACAAGAAGTGGAATAGCAGCAATTACACATGGTGCTCTCCAGGGAC  
TAGCTTATTTACATTCTCATACCATGATCCATAGAGATATCAAAGCAGGAAATATCCTTC  
TGACAGAACCAGGCCAAGTGAAACTTGCTGACTTTGGATCTGCTTCCATGGCTTCCCCTG  
CCAATTCTTTTGTGGGAACACCATATTGGATGGCCCCAGAAGTAATTTTAGCCATGGATG  
AAGGACAGTATGATGGCAAAGTTGATGTATGGTCTCTTGGAATAACGTGTATTGAATTAG  
CCGAGAGGAAGCCTCCTTTATTTAATATGAATGCAATGAGTGCCTTATATCACATAGCCC  
AAAATGAATCCCCTACACTACAATCTAATATGAATGATTCTTGCCTCCAGAAAATCCCTC  
AAGATCGCCCTACATCAGAGGAACTTTTAAAGCACATGTTTGTCTTCGAGAGCGCCCTG  
AAACAGTGTTAATAGATCTTATTCAAAGGACAAAGGATGCAGTAAGAGAGCTGGACAATC  
TGCAGTATCGAAAGATGAAGAACTCCTTTTCCAGGAGGCACATAATGGGCCAGCGGTAG  
AAGCACAGGAAGAAGAGGAGGAGCAAGATCATGGTGTGGCCGAACAGGAACAGTGAATA  
GTGTTGGAAGCAATCAGTCTATCCCTAGTATGTCTATCAGTGCCAGCAGTCAAAGCAGCA  
GTGTTAATAGTCTTCCAGATGCATCAGATGACAAGAGTGAGCTAGACATGATGGAGGGAG  
ACCATACAGTGATGTCTAACAGTTCTGTCTCCACTTAAACCTGAGGAGGAAAATTACC  
AGGAAGAAGGAGATCCTAGAACAAGAGCATCAGACCCACAGTCTCCCCCTCAGGTGTCTC  
GTCACAAGTCACATTATCGTAATAGAGAACACTTTGCAACCATACGAACAGCATCACTGG  
TTACAAGACAGATGCAAGAACATGAGCAGGACTCTGAACTTAGAGAACAGATGTCTGGTT  
ATAAGCGGATGAGGCGACAGCATCAAAGCAGCTGATGACGCTGGAAAAATAAACTGAAGG  
CAGAGATGGACGAACATCGGCTCAGATTAGACAAAGATCTTGAAACTCAGCGTAACAATT  
TCGCTGCAGAAATGGAGAACTTATTAAGAAACACCAAGCTGCTATGGAAAAAGAGGCTA  
AAGTGATGGCCAATGAGGAGAAAAAATTCAGCAACACATTCAGGCTCAACAGAAAAAAG  
AACTGAATAGCTTTTTTGGAGTCTCAAAAAAGAGAATATAAACTTCGCAAAGAGCAGCTTA  
AGGAGGAGCTGAATGAAAACCAGAGCACACCTAAAAAAGAAAAGCAGGAATGGCTTTCAA  
AGCAGAAGGAGAATATACAGCATTTTCAGGCAGAAGAAGAAGCTAATCTTCTTCGACGTC  
AAAGGCAGTATCTAGAGCTAGAATGTCGTCGCTTCAAAGAAGAATGTTACTTGGGCGAC  
ATAACTTGGAACAGGACCTTGTCAGGGAGGAGTTAAACAAAAGGCAGACTCAAAGGACT  
TGGAACATGCAATGCTATTGCGACAGCATGAATCAATGCAAGAACTGGAGTTTCGCCATC  
TCAACACTATTCAGAAGATGCGCTGTGAGTTGATCAGACTGCAGCATCAAACCTGAGCTCA  
CTAACAGCTAGAGTACAATAAGAGAAGGGAACGGGAACTGAGGCGAAAACATGTCATGG

**Fig. 9R**

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AAGTTCGACAACAACCTAAGAGTCTGAAGTCTAAAGAACTCCAAATAAAAAAGCAGTTTC  
AGGATACCTGCAAAATTCAAACCAGACAGTACAAAGCATTAAAGGAATCACCTACTGGAGA  
CTACACCAAAGAATGAGCACAAAGCAATC

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CGAAGCCACAGCCCGAGCCCGAGCCCGAGCCCGAGCCGGCGCCACCGCGCCCCCGGCCAT  
GGCTTTTGCCAATTTCCGCCGCATCCTGCGCCTGTCTACCTTCGAGAAGAGAAAGTCCCG  
CGAATATGAGCACGTCCGCCGCGACCTGGACCCCAACGAGGTGTGGGAGATCGTGGGCGA  
GCTGGGCGACGGCGCCTTCGGCAAGGTTTACAAGGCCAAGAATAAGGAGACGGGTGCTTT  
GGCTGCGGCCAAAGTCATTGAAACCAAGAGTGAGGAGGAGCTGGAGGACTACATCGTGGA  
GATTGAGATCCTGGCCACCTGCGACCACCCCTACATTGTGAAGCTCCTGGGAGCCTACTA  
TCACGACGGGAAGCTGTGGATCATGATTGAGTTCTGTCCAGGGGGAGCCGTGGACGCCAT  
CATGCTGGAGCTGGACAGAGGCCTCACGGAGCCCCAGATACAGGTGGTTTGCCGCCAGAT  
GCTAGAAGCCCTCAACTTCCTGCACAGCAAGAGGATCATCCACCGAGATCTGAAAGCTGG  
CAACGTGCTGATGACCCTCGAGGGAGACATCAGGCTGGCTGACTTTGGTGTGTCTGCCAA  
GAATCTGAAGACTCTACAGAAACGAGATTCCTTCATCGGCACGCCTTACTGGATGGCCCC  
CGAGGTGGTCATGTGTGAGACCATGAAAGACACGCCCTACGACTACAAAGCCGACATCTG  
GTCCCTGGGCATCACGCTGATTGAGATGGCCCAGATCGAGCCGCCACACCACGAGCTCAA  
CCCCATGCGGGTCCTGCTAAAGATCGCCAAGTCGGACCCTCCACGCTGCTCACGCCCTC  
CAAGTGCTGTAGAGTTCCGTGACTTCCTGAAGATAGCCCTGGATAAGAACCCAGAAAC  
CCGACCCAGTGCCGCGCAGCTGCTGGAGCATCCCTTCGTCAGCAGCATCACCAGTAACAA  
GGCTCTGCGGGAGCTGGTGGCTGAGGCCAAGGCCGAGGTGATGGAAGAGATCGAAGACGG  
CCGGGATGAGGGGGAAGAGGAGGACGCCGTGGATGCCGCCTCCACCCTGGAGAACCATA  
TCAGAACTCCTCTGAGGTGAGTCCGCCAAGCCTCAATGCTGACAAGCCTCTCGAGGAGTC  
ACCTTCCACCCCGCTGGCACCCAGCCAGTCTCAGGACAGTGTGAATGAGCCCTGCAGCCA  
GCCCTCTGGGGACAGATCCCTCCAAACCACAGTCCCCCAGTCGTGGCCCCCTGGAAATGA  
GAACGGCCTGGCAGTGCCTGTGCCCTGCGGAAGTCCCGACCCGTGTCAATGGATGCCAG  
AATTCAGGTAGCCCAGGAGAAGCAAGTTGCTGAGCAGGGTGGGGACCTCAGCCCAGCAGC  
CAACAGATCTCAAAAGGCCAGCCAGAGCCGGCCCAACAGCAGCGCCCTGGAGACCTTGGG  
TGGGGAGAAGCTGGCCAATGGCAGCCTGGAGCCACCTGCCAGGCAGCTCCAGGGCCTTC  
CAAGAGGGACTCGGACTGCAGCAGCCTCTGCACCTCTGAGAGCATGGACTATGGTACCAA  
TCTCTCCACTGACCTGTGCTGAACAAAGAGATGGGCTCTCTGTCCATCAAGGACCCGAA  
ACTGTACAAAAAAACCTCAAGCGGACACGCAAATTTGTGGTGGATGGTGTGGAGGTGAG  
CATCACCCACCTCCAAGATCATCAGCGAAGATGAGAAGAAGGATGAGGAGATGAGATTTCT  
CAGGCGCCAGGAACTCCGAGAGCTTCGGCTGCTCCAGAAAGAAGAGCATCGGAACCAGAC  
CCAGCTGAGTAACAAGCATGAGCTGCAGCTGGAGCAAATGCATAAACGTTTTGAACAGGA  
AATCAACGCCAAGAAGAAGTTCTTTGACACGGAATTAGAGAACCTGGAGCGTCAGCAAAA  
GCAGCAAGTGGAGAAGATGGAGCAAGACCATGCCGTGCGCCGCCGGGAGGAGGCCAGGCG

**Fig. 9S**

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GATCCGCCTGGAGCAGGATCGGGACTACACCAGGTTCCAAGAGCAGCTCAAACCTGATGAA  
GAAAGAGGTGAAGAACGAGGTGGAGAAGCTCCCCGACAGCAGCGGAAGGAAAGCATGAA  
GCAGAAGATGGAGGAGCACACGCAGAAAAAGCAGCTTCTTGACCGGGACTTTGTAGCCAA  
GCAGAAGGAGGACCTGGAGCTGGCCATGAAGAGGCTCACCACCGACAACAGGCGGGAGAT  
CTGTGACAAGGAGCGCGAGTGCCTCATGAAGAAGCAGGAGCTCCTTCGAGACCGGGAAGC  
AGCCCTGTGGGAGATGGAAGAGCACCAGCTGCAGGAGAGGCACCAGCTGGTGAAGCAGCA  
GCTCAAAGACCAGTACTTCTCCAGCGGCACGAGCTGCTGCGCAAGCATGAGAAGGAGCG  
GGAGCAGATGCAGCGCTACAACCAGCGCATGATAGAGCAGCTGAAGGTGCGGCAGCAACA  
GGAAAAGGCGCGGCTGCCAAGATCCAGAGGAGTGAGGGCAAGACGCGCATGGCCATGTA  
CAAGAAGAGCCTCCACATCAACGGCGGGGGCAGCGCAGCTGAGCAGCGTGAGAAGATCAA  
GCAGTTCTCCAGCAGGAGGAGAAGAGGCAGAAAGTCGGAGCGGCTGCAGCAACAGCAGAA  
ACACGAGAACCAGATGCGGGACATGCTGGCGCAGTGCGAGAGCAACATGAGCGAGCTGCA  
GCAGCTGCAGAAATGAAAAGTGCCACCTCCTGGTAGAGCACGAAACCCAGAAACTGAAGGC  
CCTGGATGAGAGCCATAACCAGAACCTGAAGGAAT

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CGTTCTTGGGCTTCCCGCTCCGCAGGCCTGCGGAGGACTGGCCCAGCAAGGTCCCAGGTC  
TTCCCTCTCCTTAGCGCCTAAGAGAGAGGGCCAGTGCGGGTGAGGAGTCGCGAGGAAGAG  
GCGGAAGGCGCCGGAAGGCACCATGTTCCGCAAGAAAAAGAAGAAACGCCCTGAGATCTC  
AGCGCCACAGAACTTCCAGCACCGTGTCACACCTCCTTCGACCCCAAAGAAGGCAAGTT  
TGTGGGCCTCCCCCACAATGGCAGAACATCCTGGACACACTGCGGGCGCCCCAAGCCCGT  
GGTGGACCCTTCGCGAATCACACGGGTGCAGCTCCAGCCCATGAAGACAGTGGTGCGGGG  
CAGCGCGATGCCTGTGGATGGCTACATCTCGGGGCTGCTCAACGACATCCAGAAGTTGTC  
AGTCATCAGCTCCAACACCCTGCGTGGCCGCAGCCCCACCAGCCGGCGGGGCACAGTC  
CCTGGGGCTGCTGGGGGATGAGCACTGGGCCACCGACCCAGACATGTACCTCCAGAGCCC  
CCAGTCTGAGCGCACTGACCCCCACGGCCTTACCTCAGCTGCAACGGGGGCACACCAGC  
AGGCCACAAGCAGATGCCGTGGCCCGAGCCACAGAGCCCACGGGTCTTGCCCAATGGGCT  
GGCTGCAAAGGCACAGTCCCTGGGCCCCGCCGAGTTTCAGGGTGCTCGCAGCGCTGTCT  
GCAGCTGGGTGCCTGCCTGCAGAGCTCCCCACCAGGAGCCTCGCCCCCAGGGGCACCAA  
TAGGCATGGAATGAAGGCTGCCAAGCATGGCTCTGAGGAGGCCCCGGCCACAGTCTGCCT  
GGTGGGCTCAGCCACAGGCAGGCCAGGTGGGGAAGGCAGCCCTAGCCCTAAGACCCGGGA  
GAGCAGCCTGAAGCGCAGGCTATTCCGAAGCATGTTCTGTCCACTGCTGCCACAGCCCC  
TCCAAGCAGCAGCAAGCCAGGCCCTCCACCACAGAGCAAGCCCAACTCCTCTTTCGACC  
GCCGCAGAAAGACAACCCCCCAAGCCTGGTGGCCAAGGCCCAGTCCTTGCCCTCGGACCA  
GCCGGTGGGGACCTTCAGCCCTCTGACCACTTCGGATACCAGCAGCCCCCAGAAGTCCCT  
CCGCACAGCCCCGGCCACAGGCCAGCTTCCAGGCCGGTCTTCCCCAGCGGGATCCCCCG  
CACCTGGCACGCCCAGATCAGCACCAGCAACCTGTACCTGCCCCAGGACCCACGGTTGC  
CAAGGGTGCCTGGCTGGTGAGGACACAGGTGTTGTGACACATGAGCAGTTCAAGGCTGC

**Fig. 9T**

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GCTCAGGATGGTGGTGGACCAGGGTGACCCCGGCTGCTGCTGGACAGCTACGTGAAGAT  
TGGCGAGGGCTCCACCGGCATCGTCTGCTTGGCCCGGGAGAAGCACTCGGGCCGCCAGGT  
GGCCGTCAAGATGATGGACCTCAGGAAGCAGCAGCGCAGGGAGCTGCTCTTCAACGAGGT  
GGTGATCATGCGGGACTACCAGCACTTCAACGTGGTGGAGATGTACAAGAGCTACCTGGT  
GGGCGAGGAGCTGTGGGTGCTCATGGAGTTCTGCAGGGAGGAGCCCTCACAGACATCGT  
CTCCCAAGTCAGGCTGAATGAGGAGCAGATTGCCACTGTGTGTGAGGCTGTGCTGCAGGC  
CCTGGCCTACCTGCATGCTCAGGGTGTCTATCCACCGGGACATCAAGAGTGACTCCATCCT  
GCTGACCCTCGATGGCAGGGTGAAGCTCTCGGACTTTCGGATTCTGTGCTCAGATCAGCAA  
AGACGTCCCTAAGAGGAAGTCCCTGGTGGGAACCCCTACTGGATGGCTCCTGAAGTGAT  
CTCCAGGTCTTTGTATGCCACTGAGGTGGATATCTGGTCTCTGGGCATCATGGTGATTGA  
GATGGTAGATGGGGAGGCCACCGTACTTCAGTGACTCCCCAGTGCAAGCCATGAAGAGGCT  
CCGGGACAGCCCCCACCAAGCTGAAAACTCTCACAAGGTCTCCCCAGTGCTGCGAGA  
CTTCCTGGAGCGGATGCTGGTGCGGGACCCCAAGAGAGAGCCACAGCCCAGGAGCTCCT  
AGACCACCCCTTCTGCTGCAGACAGGGCTACCTGAGTGCCCTGGTGGCCCTGATCCAGCT  
CTACCGAAAGCAGACCTCCACCTGCTGAGCCACCCCAAGTATGCCTGCCACCTACGCCC  
ACAGGCAGGGCACACTGGGCAGCCAGCCTGCCGGCAGGACTTGCCTGCCTCCTCCTCTCA  
GTATTCTCTCCAAAGATTGAAATGTGAAGCCCCAGCCCCACCTCTGCCCTTCAGCCTAC  
TGGGCCAGGCCGGACCTGCCCCCTCAGTGTCTCTCCCTCCCGAGTCCCCAGATGGAGACC  
CCTTTCTACAGGATGACCCCTTGATATTTGCACAGGGATATTTCTAAGAAACGCAGAGGC  
CAGCGTTCCTGGCCTCTGCAGCCAACACAGTAGAAAAGGCTGCTGTGGTTTTTTAAAGGC  
AGTTGTCCACTAGTGTCTAGGCCACTGCAGAGGGCAGACTGCTGGTCTCCACAGATACC  
TGCTGTTCTCAGCTCCAGCTTCAAACCTCGAGTCTCGAGAGGGCCACGGGGTGGTTTTTA  
TGACCGGAATCCCGCTTCTCCCTCACGTCTGATGTCTGAAGGTGCAGTCCCACCTGTA  
CAGCCCTCCCCGCCAAGAAGTGTGAATGGCCTGCTCCAGGCCATGGCTGGGGGCAGGGA  
GTGAGGGGACAATTTCTGAGTGAAAGAGAAAGAATGGGGTCGGTGGTGAAGGTGCTCTCA  
CTTTACAGAATGGAGAGAACATCGTGTGTGTGTGTGTGTGTGTGTGTGTGTGTGTGTGTG  
TG  
CCTCCAGGTCACCCACAGCCAGTTTCAGGAAGGCTGCCCCCTCTCTCCCACTAAGTTCTGG  
CCTGAAGGGACCTGCTTTCTTGGCCTGGCTTCCACCTCTCCACTCCTGTGTCTACCTGGC  
CAGTGGAGTGGTCCATGCTAAGTCTAACACTCCTGGGAGCTCAGGAGGCTTCTGAGCTTC  
TCCTGTACTGTGCATCGTGAGGGCCAGAGACAGGAATGTAAGGATTGGCAACTGTGTTAC  
CTTTCAAGTTTATCTCAATAACCAGGTCATCAGGGACCCATTGTTCTCTTCAGAACCTTA  
TCTGGGAGAGAAGGCGAACCACTCCGGGTTTCCATCATGTCAAGGTCACAGGCATCCAT  
GTGTGCAAACCATCTGCCCCAGCTGCCTCCACAGACTGCTGTCTCCTTGTCTCCTCGGC  
CCTGCCCCACTTCAGGGCTGCTGTGAGATGGAATTCCAGGAAAGAACTTCAGGTGTCTGG  
ACCTTTTCTATCTAGATAATATTTTTAGATTCTTCTGCTCCCTAGTGACCTACCTGGGGG  
CAAAGAAATTGCAAGGACTTTTTTTTAAAGGGTCAGAGTTTTCAAAACAAAAGCATCTTCC  
CTAGAAATTTTTGTGAATTGTTTGCACCTTGTGCCTGTTTTAAATTAAATTGAGTGTTCAA

**Fig. 9U**

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AGCC

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GGCCAGTGGGGCGAAACTGGCAGCTGGCCGGCCCTTTAACACCTACCCGAGGGCTGACAC  
GGACCACCCATCCCGGGGTGCCAGGGGGAGCCTCATGACGTGGCCCCCTAACGGGGCCATC  
AGCGGGGGGCTGGCCATCCCCCAGTCCTCCTCCTCCTCCTCCCGGCCTCCCACCCGAGC  
CCGAGGTGCCCCCAGCCCTGGAGTGCTGGGACCCACGCCTCAGAGCCCCAGCTGGCCCC  
TCCAGCCTGCACCCCCCGCCGCCCTGCTGTTCTGCGGGCCCCCTGGCCCCCGCTCACCACA  
GCGGGAGCCACAGCGAGTATCCCATGAGCAGTTCCGGGCTGCCCTGCAGCTGGTGGTGA  
CCCAGGCGACCCCCGCTCCTACCTGGACAACCTTCATCAAGATTGGCGAGGGCTCCACGGG  
CATCGTGTGCATCGCCACCGTGCGCAGCTCGGGCAAGCTGGTGGCCGTCAAGAAGATGGA  
CCTGCGCAAGCAGCAGAGGGCGGAGCTGCTCTTCAACGAGGTGGTAATCATGAGGGACTA  
CCAGCACGAGAATGTGGTGGAGATGTACAACAGCTACCTGGTGGGGGACGAGCTCTGGGT  
GGTCATGGAGTTCTTGGAAAGGAGGCGCCCTCACCGACATCGTCACCCACACCAGGATGAA  
CGAGGAGCAGATCGCGGCCGTGTGCCTTGCAAGTGCTGCAGGCCCTGTGCGTGCTCCACGC  
CCAGGGCGTCATCCACCGGGACATCAAGAGCGACTCGATCCTGCTGACCCATGATGGCAG  
GGTGAAGCTGTCAGACTTTGGGTTCTGCGCCCAGGTGAGCAAGGAAGTGCCCCGAAGGAA  
GTCGCTGGTCGGCACGCCCTACTGGATGGCCCCAGAGCTCATCTCCCGCCTTCCCTACGG  
GCCAGAGGTAGACATCTGGTCGCTGGGGATAATGGTGATTGAGATGGTGGACGGAGAGCC  
CCCCTACTTCAACGAGCCACCCCTCAAAGCCATGAAGATGATTGCGGGACAACCTGCCACC  
CCGACTGAAGAACCTGCACAAGGTGTCGCCATCCCTGAAGGGCTTCTCTGGACCGCCTGCT  
GGTGCGAGACCCTGCCCAGCGGGCCACGGCAGCCGAGCTGCTGAAGCACCCATTCTTGGC  
CAAGGCAGGGCCGCTGCCAGCATCGTGCCCTCATGCGCCAGAACCGCACCCAGATGAGG  
CCCAGCGCCCTTCCCCTCAACCAAGAGCCCCCCCCGGGTACCCCCCGCCCCACTGAGGCC  
AGTAGGGGGGCCAGGCCTCCCACTCCTCCCAGCCCCGGGAGATGCTCCGCGTGGCACCACCC  
TCCTTGCTGGGGGTAGATGAGACCTACTACTGAACTCCAGTTTTTGATCTCGTGACTTTT  
AGAAAAACACAGGGACTCGTGGGAGCAAGCGAGGCTCCCAGGACCCCCACCCTCTGGGAC  
AGGCCCTCCCCCATGTTCTTCTGTCTCCAGGAAGGGCAGCGGCCCTCCCATCACTGGAAG  
TCTGCAGTGGGGGTGCTGCTGGGGGTGGAGAGAACACTAAGAGGTGAACATGTATGAGTGTG  
TGCACGCGTGTGAGTGTGCATGTGTGTGTGTGTGCAAAGGTCCAGCCACCCCGTCCTCCA  
GCCCCGAAGGGGTGTCTGGCGCCTTGCTGACACCCAGCCCCCTCTCCCCCTGAGCCATT  
GTGGGGGTGATCATGAATGTCCGAAGAGTGGCCTTTTCCCGTAGCCCTGCGCCCCCTTT  
CTGTGGCTGGATGGGAGACAGGTCAGGGCCCCCCCCACCCTCTCCAGCCCCTGCAGCAAAT  
GACTACTGCACCTGGACAGCCTCCTCTTTTCTAGAAGTCTATTTATATTGTCAATTTTATA  
AACTCTAGCCCCCTGCCCTTATTGGGGGACAGATGGTCCCTGTCCTGCGGGGTGGCCCTG  
GCAGAACCACTGCCTGAAGAACCAGGTTCTTGGCCGTCAGCGCAGCCCCAGCCCCGCCCCA  
CCCCTGCCTCGAGTTAGTTTTACAATTAACATTGTCTTGTGTTTTGTGAAAAAAAAAAAAA  
AAAAAAAAAA

**Fig. 9V**  
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>STLK5\_h  
 MSSFLPEGGCYELLTVIGKGFEDLMTVNLARYKPTGEYVTVRRINLEACSNEMVTFLQGELHVSCLFNHPNIVPYRATFI  
 ADNELWVVTSMAYGSAKDLICTHFMGDMNELAIAIYLQGVLKALDYIHHMGYVHRSVKASHILISVDGKVYLSGLRSNL  
 SMISHGQRQRVVHDFPKYSVKVLPWLSPEVLQQLQGYDAKSDIYSVGITACELANGHVPFKDMPATQMLLEKLN GTVPC  
 LLDTSIPAEELTMSPSRSVANSGLSDSLTTSTPRPSNGDSPSHPHYHRTFSPHFHFVEQCQLQRNPDARPSASTLLNHSF  
 FKQIKRRASEALPELLRPVPTITNFEQSQDHSIGIFGLVTNLEELEVDWDEF

>STLK6\_h  
 MSLDCCFCTSRQTQVESLRPEKQSETSIHQYLVDEPTLSWSRPSRASEVLCSTNVSHYELQVEIGRGFDNLT SVHLARHT  
 PTGTLVTIKITNLENCNEERLKAQKAVILSHFFRHPNITTYTWTFTVGSWLWVISPFMAYGASQLLRTYFPEGMSETL  
 IRNILFGAVRGLNYLHQNGCIHRSIKASHILISGDGLVTL SGLSHLSLVKHGQRHRAVYDFPQFSTSVQPWLSPELLRQ  
 DLHGYNVKS DIYSVGITACELASGQVPFQDMHRTQMLLQKLKGPYSPLDISIFPQSESRMKNSSQSGVDSGIGESVLVSS  
 GHTVNSDRLHTPSSKTFSPAFFSLVQLCLQQDPEKRPSASSLLSHVFFKQMKESQDSILSLPPAYNKPSSISLPPVLP  
 WTEPECDFPDEKDSYWEF

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>STLK7\_h  
 NRDDYELQEVIGSGATAVVQAA YCAPKKEKVAIKRINLEKCQTSMDLELLKEIQAMSQCHHPNIVSYTTSFVVVKDELWLVM  
 KLLSGGSVLDIIKHIVAKGEHKS

>ZC4\_h  
 MAGPGGWRDREVTDLGHLPDPTGIFSLDKTIGLTGTYGRIYGLGHEKTGAFTAVKVMNARKDEEEDLRTLENL LRKYSFHK  
 NIVSYGAFKKLSPPGQRHLWMVMELCAAGSVTDVVRMTSNQSLKEDWIAIYICREILQGLAHLHAHRV IHRDIKGGQNVL  
 LTHNAEVKLVD FGVSAQVSRINGRRNSFIGTPYWMAP EVIDCDEDPRRSYDYRSDVWSVGITAIEMAEGAPPLCNLQPLE  
 ALFVILRESAPT VKSSGWSRKHFHFM EKCTIKNFLFRPTSANMLQHPFVRDIKNERHVVESLTRHLTGIIKKRQKKEQAR  
 EKSKSVSTLRQALAKRLSPKRFRAKSSWRPEKLELSDLEARRQRRRWEDIFNQHEEELRQVDKDEKDESSDNDEVFHS

Fig. 10A

IQAEVQIEPLKPYISNPKKIEVQERSPSVPNNQDHAHVKFSSSVQPSRLLEQAQKPIDIRQSSQNRQNWLAASGDSKH  
 KILAGKTSYCLTIYISEVKKEEFQEGMNQKCQGAQVGLGPEGHCIWQLGESSSEESPVTRRSQSSPPYSTIDQKLLV  
 DIHVPDGFVKISPPVYLTNEWVGYNALSEIFRNDWLTAPVVIQPPPEEDGYVELYDASADTDGDDDDDESNDTFEDTYD  
 HANGNDDLQNVQDQANDVCKDHDDNNKFVDDVNNYYEAPSCPRASYGRDGSCKQDGYDGSRGKEEAYRGYGSHTANRS  
 HGGSAASEDNAAIGDQEEHAANIGSERRGSEGGGKGVVRTSEESGALGLNGEENCSETDGPGLKRPAQDFFEYLQEEPG  
 GGNEASNAIDSGAAPSDHESDNKDISESTQSDFSANHSSPSKSGMSADANFASAILYAGFVEVPEESPQKQPSSEVNV  
 NPLYVSPACKKPLIHMYEKEFTSEICCSLWGVNLLGTRSNLYLMDRSGKADITKLIRRRPFRQIQVLEPLNLLITISG  
 HKNRLRVYHLTWLRNKILNNDPESKRREQEEMLKTEEACKAIDKLTGCEHFSVLQHEETTYIAIALKSSIHLYAWAPKSF  
 ESTAIKVFPITLDHKPVTVDLAIGSEKRLKIFFSSADGYHLIDAESEVMSDVTLPKNPLEIIIPQNIILPDCLGIGMMLT  
 FNAEALSVEANEQLFKKILEMWKDIPISSIAFECTQRTTGWGQKAIIEVRSLSQSRVLESELKRRSIKKLRFCLCTRGDKLFFT  
 STLNRNHSRVYFMTLGKLEELQSNYDV

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&gt;PAK5\_h

MFGKRKRREIISAPSNFEHRVHTGFDQHEQKFTGLPRQWQSLIEESARRPKPLVDPACITSIQPGAPKTIIVRGSKGAKDG  
 ALTLLDEFENMSVTRNSLRDSPPPPARARQENGMPPEEPATTARGGPGKAGSRGFAGHSEAGGGSGDRRRRAGPEKRP  
 KSSREGSGGPQESSRDKRPLSGPDVGTQPAGLASGAKLAAGRPFNTYPRADTDHPSRGAQGEPHDVAPNGPSAGGLAIP  
 QSSSSSRPPTRARGAPSPGVLGPHASEPQLAPPACTPAAPAVPGPPGPRSPQREPQRVSHQFRAALQLVVDPGDPRSY  
 LDNFIKIGEGSTGIVCIATVRSSGKLVAVKKMDLRKQRRRELLFNEVVIMRDYQHENVVEMYNLYVGDDELWVVMFELEG  
 GALTDIVTHTRMNEEQIAAVCLAVLQALSVLHAQGVIHREDIKSDSILLTHDGRVKLSDFGFCQVSKVPRRKSIVGTPY  
 WMAPELISRLPYGPEVDIWSLGIMVIEMVDGEPYPFNEPPLKAMKMIRDNLPPRLKNLHKVSPSLKGFDRLLVDRDPAQR  
 ATAAELLKHPFLAKAGPPASIVPLMRQNRTR

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MAFANFRRIRLSTFEKRKSREYEHVRRDLDPNEVWEIVGELGDGAFGKVYKAKNKETGALAAAKVIETKSEEELEDYIV  
 EIEILATCDHPYIVKLLGAYYHDGKLIWMIEFCPGGAVDAIMLELDRLGTEPQIQVVCVRQMLEALNFLHSKRRIIHRDLKA

Fig. 10B



GNVLMTLEGDIRLADFGVSAKNLKTLLQKRDSFIGTPYWMapevVMCETmKDTpYdYKADIwSLGITLIEMaQIEpPHHEL  
 NPMRVLLKIAKSDPPTLLTPSKWSVEFRDFLKIALDKNPetrPSAAQLLEHPFVSSITSNKALRELVAEAKAEVMEEIED  
 GRDEGEEDAVDAASTLENHTQNSSEVSPPSLNADKPLEESPSTPLAPSQSDSVNEPCSQPSGDRSLQTTSPPVVAPGN  
 ENGLAVPVPLRKSRPVSMdARIQVAQEKQVAEQGGDLSPAANRSQKASQSRPNSSALETlGGEKLANGSLEPPAQAAAGP  
 SKRSDCSSLCTSESMDYGTNLSTDLSLNKEMGSLSIKDPKLYKKTlKRTRKFVVDGVEVSITTSKIISEDEKKDEEMRF  
 LRRQELRELRLlLQKEEHRNQTQLSNKHHELQLEQMhKRFEQEIINAKKKFFDTELENLERQQKQVEKMEQDHAVRRREEAR  
 RIRLEQDRDYTRFQELKLMKKEVKNEVEKLPRQQRKESMKQKMEEHTQKKQLLDRDFVAKQKEDLELAMKRLTTDNRRRE  
 ICDKERECLMKKQELLRDREAALWEMEEHQLQERHQLVKQQLKQYFLQRHELlRKHEKEREQMQRYNQRMIEQLKVRQQ  
 QEKARLPKIQRSEGKTRMAMYKKSLLHNGGSAAEQREKIKQFSQQEERQKSERLQQQKQHENQMRDMLAQCESNMSEL  
 QQLQNEKCHLLVEHETQKLKALDESHNQNLKEWRDKLPRRKKALEEDLNQKKREQEMFFKLSEEAECNPSTPSKAAKFF  
 PYSSGDAS

Fig. 10C

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GGCCAAAGACGGTCGGGGCTGCTTGCTAACTCCAGGAACAGGTTTAAAGTTTTTGAAACTGAAGTAGGTCTACACAGTAGGA  
ACTCATGTCTATTTCTTGTAAGTAAACAGAGCGAATCAGGCGGTGGGTCTCGGAAAGTTTCATTGTTGAGGGCTTAAAGAG  
ATTTGGAACTATTTGGAGACCAATGATGCGAGCTCAGAGTCAATAGCATCCTTCTCTAAACAGGAGGTCTAGTAGCTT  
TCTGCCAGAGGGAGGTGTTACGAGCTGCTCACTGTGATAGGCAAGGATTTGAGGACCTGATGACTGTGAATCTAGCAA  
GGTACAAACCAACAGGAGAGTACGTGACTGTACGGAGGATTAACTTAGAAGCTTGTTCCTCAATGAGATGGTAACATTCTTG  
CAGGGCAGCTGCTGCTCCAAACTCTTCAACCATCCCAATATCGTGCCATATCGAGGCCACTTTATTGACAGACAATGA  
GCTGTGGGTGTACATCATTCATGGCATAACGGTTCTGCAAAAGATCTCATCTGTACACACTTTCATGGATGGCATGAATG  
AGCTGGCGATTGCTTACATCCTGCAGGGGGTGTCTGAAGGCCCTCGACTACATCCACCACATGGGATATGTACACAGGAGT  
GTCAAAGCCAGCCACATCCTGATCTCTGTGGATGGGAAGTCTACCTGTCTGGTTTGCAGCAACCTCAGCATGATAAG  
CCATGGGCAGCGGCAGGTGGTCCACGATTTTCCCAAGTACAGTGTCAAGTTCTGCCGTGGCTCAGCCCGAGGTCC  
TCCAGCAGAACTCCAGGGTTATGATGCCAAGTCTGACATCTACAGTGTGGGAATCACAGCCTGTGAACCTGGCCAAACGGC  
CATGTCCCTTTAAGGATATGCTGCCACCCAGATGCTGTAGAGAACTGAACGGCACAGTGCCTGCTGCTTGGATAC  
CAGCACCATCCCCGCTGAGGAGCTGACCATGAGCCCTCCACCCCTACCAACCGAACCTTCTCCCCACCTTCCACCACTT  
CCAGCACCCCGGCCCTCACAACGGTGACTCGCCCTCCACCCCTACCAACCGAACCTTCTCCCCACCTTCCACCACTT  
GTGGAGCAGTGCCCTCAGCGCAACCCGGATGCCAGGCCAGTGCCAGCACCTCCTGAACCACTCTTCTTCAAGCAGAT  
CAAGCAGCTGCCCTCAGAGGCTTTGCCCCGAATTGCTTCGTCTGTACCCCTACCAATTTTGAAGGCGAGCCAGTCTC  
AGGACCACAGTGGATCTTTGGCTGGTAAACAACCTGGAGAGCTGGAGGTGGACGATTGGGAGTTCTGAGCCTCTGCA  
AACTGTGCGCATTTCTCCAGCCAGGGATGCAGAGGCCACCCAGAGGCCCTTCTGAGGCCGCCACATTCCCGCCCTCT  
GGGCAGATTGGGTAGAAAGGACATTTCTCCAGGAAAGTTGACTGCTGACTGATTGGGAAAGAAATCCTGGAGAGATACT  
TCACTGCTCCAGGCTTTTGAGACACAAGGGAATCTCAACAACAGGGATCAGGAGGGTCCAAAGCCGACATTCCCAAGTC  
CTGTGAGCTCAGGTGACCTCTCCGAGAAAGAGATGCTGCTCTGGCCCTGGGAGCTGAATTCCAAGCCAGGGTTTGG  
CTCCTTAAACCCGAGGACCGCCACCTCTTCCAGTGCTTGGACCCAGCCTCATTTCTAATTTGCTCTCAGATGCTT  
CAGATGCTATAGGTAGTGAAAGGCAAGTAGTAGCTGCCCTCCCTTCCCTCAGACCTCTCCCTCATAAATCCAGAG  
GAAGGGCATTTCTGTCTTTTAAAGCACAGACTAAGGCTGGACAGTCCATCTTATCCCTCTTCTGGCTTGGGCCCTGAC

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**Fig. 11A**

ACCTAAGTCTTTCCACGGTTTATGTGTGCGCTCATTCCTTTCCACCAAGAATCCATCTTAGCGCCTCCTGCCAGCTG  
 CCTGGTGCTTTCTCCAAAGGGCCCATCAGTGTCTTGCCCTAGCTTGAGGGCTTAAAGTCCCTTATGCTGTGTAGTTTCGTTGT  
 CAGAACAAATTAAATTTTCAGAGACGCTG

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AAGGAAGATAAAACAAAGCCCTTCTTTGGAATAGATGGATTTTGTCACTTTTCTGTGTGAACATAAAGTGATTCAATGTCT  
 CTTTGGATTGCTTCTGCACCTTCAAGAACACAAAGTTGAATCACTCAGACCTGAAAAACAGTCTGAACACAGTATCCATCA  
 ATACTGGTTGATGAGCCAAACCTTTCTCTGTCACGTCCATCCACTAGAGCCAGTGAAGTACTATGTTCACCAACGTTT  
 CTCACTATGAGCTCCAAGTAGAAATAGGAAGAGGATTTGACAACTTGACTTCTGTCCATCTTGCACGGCATACTCCACG  
 GAAACACTGGTAACATAAAATTACAAATCTGGAAACTGCAATGAAGAACGCTGAAAGCTTTACAGAAAGCCGTGAT  
 TCTATCCACCTTTTCCGGCATCCCAATATTACAACCTTATGGACAGTTTTCACCTGTGGCAGCTGGCTTTGGGTTATTT  
 CTCCATTTATGGCCTATGGTTCAGCAAGTCAACTCTTGAGGACCTATTTCTGAAGGAATGAGTGAAACTTTAATAAGA  
 AACATTTCTTTGGAGCCGTGAGAGGGTTGAACCTATCTGCACCAAAATGGCTGTATTCACAGGAGTATTAAAGCCAGCCCA  
 TATCCTCATTTCTGGTGATGGCCTAGTGACCTCTCTGGCCTTTCCCATCTGCATAGTTTGGTTAAGCATGGACAGAGGC  
 ATAGGGCTGTGTATGATTTCCACAGTTTCAGCACATCAGTGCCGCTGGTCCAGAACTACTGAGACAGGATTTA  
 CATGGGTATAATGTGAAGTCAGATATTACAGTGTGGGATTACAGCATGTGAATTAGCCAGTGGGCAGGTGCCCTTCCCA  
 GGACATGCATAGAACTCAGATGCTGTTACAGAAACTGAAAGTCTCTCTTATAGCCCATTTGGATATCAGTATTTTCCCTC  
 AATCAGAAATCCAGAAATGCCAGTCAGGTGTAGACTCTGGGATTGGAGAAAGTGTGCTTGTCTCCAGTGGAACT  
 CACACAGTAAATAGTGACCGATTACACACACCATCCTCAAAACCTTCTCTCCTGCCCTTCTTAGCTTGGTACAGCTCTG  
 TTTGCAACAAGATCCTGAGAAAGGCCATCAGCAAGCAGTTTATGTGCCATGTTTCTTCAACACAGATGAAAGAAAGAA  
 GCCAGGATTCAATACTTTCACCTGTGCTCTGCTTATAACAAGCCATCAATATCATTTGCCCTCCAGTGTACCTTGGACT  
 GAGCCAGAATGTGATTTTCCCTGATGAAAAAAGACTCATACTGGGAATTTCTAGGGCTGCCAAATCATTTTATGTCCCTATATA  
 CTTGACACTTTCTCTGCTGCTTTTCTCTGATTTCTAGGTACAAATACCAGAAATTATATACTTGAAAAATACAGTTGGT  
 GCACTGGAGAACTATTATTTAAACCACTCTGTTCAAAGGGCACCAAGTTGTAGTCCCTCTGTTTCGCCACAGAGTACT  
 ATGACAAGGAAACATCAGAAATTACTAATCTAGCTAGTGTCAATTTTCTGGAAATTTTCTTAAGCTGTGACTAATCTT

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**Fig. 11B**

TTTATCTCTCAATAATAATTTTGTAGCCAGTTAATTTTTCAGTATTTTGTCTGTCCCTTGGGAATGGGCCCTCAGAGGAC  
 AGTGCTTCCAAGTACATCTTCTCCAGATTCTCTGGCCTTTTAAATGAGCTATTTGTTAAACCAACAGGCTAGTTTATCTT  
 ACATCAGACCCCTTTTCTGGTAGAGGGAAAATGTTTGTGCTTTTCCCTTTTCTCTGTTAATACTTATGGTAAACACCTAAC  
 TGAGCCTCACTCACTAATAATGATTCACTTGAATAATACAGAAAATTGTAATTTGCTTTTAAAGGAGGGGCTAA  
 AGTAACACTTTCCTACTTATGTAAATTATAGATCCTAAATTCACGCCACCCCGTGGAGCTCAATAAGATTTACTGAATT  
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TCAACAGGGGACGATTACGAGCTGCAGGAGGTGATCGGGAGTGGAGCAACTGCTGTAGTCCAAAGCAGCTTATTGTGCCCT  
 AAAAGGAGAAAGTGGCAATCAACGGATAAACCTTGAGAAATGTCAAACTAGCATGGATGAACCTCCTGAAAGAAATTCA  
 AGCCATGAGTCAATGCCATCATCCTAATAATTGTATCTTACTACACATCTTTTGTGTTAAAGATGAGCTGTGGCTTGTCA  
 TGAAAGCTGCTAAGTGGAGGTTCTGTTCTGGATATTATTAAGCACATTGTGGCAAAAGGGGAACACAAAAGT

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ATGGCGGGACCTGGGGGCTGGAGGGACAGGGAGGTACGGATCTGGGCCACCTGCCGGATCCAACTGGGAATATCTCACT  
 AGATAAAACCAATTGGCCTTGGTACTTATGGCAGAACTATTTGGGACTTTCATGAGAAGACTGGTGCAATTTACAGCTGTTA  
 AAGTGATGAACGCTCGTAAGGATGAGGAAGAGGATCTCAGGACTGAACCTCAACCTTCTGAGGAAGTACTCTTCCACAAA  
 AACATTGTGTCCTTCTATGGAGCATTTTCAAGCTGAGTCCCCCTGGTCAGCGGCCACCAACTTTGGATGGTGGAGTT  
 ATGTGCAGCAGGTTCCGTCACTGATGTAGTGAGAAATGACCAATCAGAGTTTAAAGAGATTGGATTGCTTATATCT  
 GCCGAGAAATCCTTCAGGGCTTAGCTCACCTTCACGCACACCGAGTAATTCACGGGACATCAAGGTCAGAAATGTGCTG  
 CTGACTCATAATGCTGAAGTAAACTGGTTGATTTTGGAGTGAGTGCCCGAGTGAGCAGAACTAATGGAAAGGAATAG  
 TTTTCATTGGGACACCATACTGGATGGCACCTGAGGTGATTGACTGTGATGAGGACCCAAAGACGCTCCTATGATTACAGAA  
 GTGATGTGGTCTGTGGGAATTACTGCCATTGAATGGCTGAAGGAGCCCTCCTCTGTGTAACTTCAACCTTGGAA  
 GCTCTCTTCGTTATTTGCGGGAAATCTGCTCCACAGTCAATCCAGCGGATGGTCCCGTAAGTCCACAAATTCATGGA  
 AAAGTGACGATAAAAAATTTCTCTGTTTCGTCTACTTCTGCAACACATGCTTCAACACCCATTGTTTCGGGATATAAAAA

**Fig. 11C**

ATGAACGACATGTTGTTGAGTCATTAAACAAGGCATCTTACTGGAATCATTAAAAAAGACAGAAAAAAGAACAGGCACGG  
 GAGAAAAAATCAAAAGTTTCTACTCTGAGGCAAGCACTGGCAAAAAGACTATCACCAAAGAGGTTTCAGGGCAAAGTTCATC  
 ATGGAGACCTGAAAAGCTTGAACTCTCGGATTTAGAAAGCCCGCAGGCAAAAGCGCCAAACGCAGATGGGAAGATATCTTTA  
 ATCAGCATGAGGAAGAAATTGAGACAAGTTGATAAAGACAAGAGAATGAATCATCAGACAATGATGAAGTATTTTCATTCTG  
 ATTCAGGCTGAAGTCCAGATAGAGCCATTGAAGCCATACATTTCAATCCIAAAAAAATTGAGGTTCAAGAGAGATCTCC  
 TTCTGTGCTAACCAACAGGATCATGCACATCATGTCAAGTTCTCTTCAAGCGTTCTCTCAGCGGTCTCTTTTGGAAACAAG  
 CTCAGAAGCCCATTTGACATCAGACAAGGAGTTGCAAAATCGTCAAAATTTGGCTGGCAGCATCAGGTGATTTCAAAAGCAC  
 AAAATTTTAGCAGGCAAAACACAGAGCTACTGTTTAAACAATTTATATTTTCAGAAAGTCAAGAAAGAAAGAAATTTCAAGAAGG  
 AATGAATCAAAAGTGTCAAGGAGCCCAAGTAGGATTAGGACCTGAAGGCCATTGTATTTTGGCAATTTGGGTGAATCTTCTT  
 CTGAGGAAGAAAGTCTGTGACTGGAAAGGAGGTCTCAGTCAATCACCCCTGTATACCTTACTATTGATCAGAAAGTTGCTGGTT  
 GACATCCATGTTCCAGATGGATTTAAAGTAGGAAAAATATCACCCCTGTATACCTTGACAAACGAATGGGTAGGCTATAA  
 TGCACTCTCTGAAATCTTCCGGAATGATTGGTTAACTCCGGCACCTGTCAATTCAGCCACTGAAGAGGATGGTGATTATG  
 TTGAACTCTATGATGCCAGTGTGATACCTGATGATGATGATGATGATGATGATGATGATGATGATGATGATGATGATGATGAT  
 CATGCCAATGGCAATGATGACTTGGATAACCCAGGTTGATCAGGCTAATGATGTTTGTAAAGACCATGATGATGACAAACA  
 TAAGTTTGTGATGATGATAATAATAATTATGAGCGCTAGTTGTCCAAGGCCAAGCTATGGCAGAGATGGAAGCT  
 GCAAGCAAGATGGTTATGATGGAAATCGTGGAAAGAGGAAGCCATCAGAGGCTATGGAAAGCCATACAGCCAAATAGAAAGC  
 CATGGAGGAAGTGCAGCCAGTGAAGACAATGCAGCCATTGGAGATCAGGAAGAACAATGCAGCCCAATATAGGCAGTGAAAG  
 AAGAGCCAGTGAGGTGATGGAGGTAAAGGAGTCTGTTGAAACCAAGTGAAGAGAGTGGAGCCCTTGGAATCAATGGAGAAG  
 AAAATTGCTCAGAGACAGATGGTCCAGGATTGAAGAGACCTGCGTCTCAGGACTTTGAATATCTACAGGAGGAGCCAGGT  
 GGTGGAAATGAGGCTCAAATGCCATTGACTCAGGTGCTGCACCGTCAAGCACCTGATCATGAGAGTGACAATAAGGACAT  
 ATCAGAAATCATCAACACAATCAGATTTTCTGCCAATCACTCATCTCTTCCAAGGTTCTGGGATGTCTGCTGATGCTA  
 ACTTTGCCAGTGCCATCTTATACGCTGGATTCTGTAGAAGTACCTGAGGAATCACCTAAGCAACCCCTCTGAAGTCAATGTT  
 AACCCACTCTATGCTCTCTCTGATGTAAAAAACCACTAATCCACATGTATGAAAAGGAGTTCACTTCTGAGATCTGCTG  
 TGGTTCTTTGTGGGAGTCAATTTGCTGTTGGGAACCCGATCTAATCTATCTGATGGACAGAAGTGGAAGGCTGACA  
 TTAATAAATTAAGGCGAAGACCATTCCGCCAGATTCAAGTCTTAGAGCCACTCAATTTGCTGATTACCATCTCAGGT

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**Fig. 11D**

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**Fig. 11E**

GAGGTGCCCCAGCCCTGGAGTGCTGGGACCCACGCGCTCAGAGCCCCCAGCTGGCCCCCTCCAGCCTGCACCCCCCGCCGCC  
 CCTGCTGTTCCCTGGGCCCCCTGGCCCCCGCTCACACAGCGGGAGCCACAGCGAGTATCCCATGAGCAGTTCCGGGGCTGC  
 CCTGCAGCTGGTGGACCCAGGCGACCCCGCTCCTACCTGGACAACTTCAAGATTGGCGAGGGCTCCACGGGCA  
 TCGTGTGCATCGCCACCGTGCGCAGCTCGGGCAAGCTGGTGGCCGTCAAGAAGATGGACCTGCGCAAGCAGCAGAGCGCC  
 GAGCTGCTCTTCAACGAGGTGGTAATCATGAGGGACTACACGACACGAGAATGTGGTGGAGATGTACAACAGCTACCTGGT  
 GGGGACGAGCTCTGGGTGCTCATGGAGTTCTTGGAGGAGGCGCCCTCACCGACATCGTCAACCCACACAGGATGAACG  
 AGGAGCAGATCGCGGCGGTGCGCTTGCAGTGCTGCGGCCCTGTGGTGCTCCAGCCCCAGGGCGTCAATCCACCGGGAC  
 ATCAAGAGCGACTCGATCCTGCTGACCCATGATGGCAGGGTGAAGCTGTCAAGCTTTGGGTTCTGCGCCAGGTGAGCAA  
 GGAAGTGCCCGAAGGAGTCGCTGGTCGACGCGCTACTGGATGGCCCGCAGAGCTCATCTCCGCGCTTCCCTACGGGC  
 CAGAGGTAGACATCTGGTCGCTGGGGATAATGGTGATTGAGATGGTGGAAGGAGCCCCCTACTTCAACGAGCCACCC  
 CTCAAAGCCATGAAGATGATTCGGGACAACTGCCACCCCGACTGAAGAACCTGCACAAGGTGTGCGCCATCCCTGAAGGG  
 CTTCTTGACCGCTGCTGGTGAGACCTTGCCAGCGGGCCACGGCAGCCGAGCTGCTGAAGCACCCATTCCTGGCCA  
 AGGCAGGGCGGCTGCCAGCATGCTGCCCTCATGCGCCAGAACCGCACAGATGAGGCCAGCGCCCTTCCCTCAACC  
 AAAGAGCCCCCGGTCACCCCGCCACTGAGGCCAGTAGGGGGCCAGGCCCTCCCACTCTCCAGCCCCGGGAGATG  
 CTCGCGTGGCACCACTCTGCTGGGGTAGATGAGACCTACTACTGAACTCCAGTTTGTGATCTCGTGACTTTTAG  
 AAAACACAGGGACTCGTGGGAGCAAGCGAGGCTCCAGGACCCCACTCTGGGACAGGCCCTCCCATGTTCTTCT  
 GTCTCCAGGAAGGCGAGCGGCCCTCCCATCACTGGAAGTCTGCAGTGGGGTCTGCTGGGGTGGAGAGACACTAAGAGG  
 TGAACATGATGAGTGTGTCACGCGTGTGAGTGTGCATGTGTGTGTGCAAGGTCCAGCCACCCCGTCTCCAGC  
 CCGCAAGGGGTGCTGGCGCCTTGCCCTGACACCCAGCCCCCTCTCCCTGAGCCCATTTGTGGGGTCGATCATGAATGTC  
 CGAAGAGTGGCCTTTTCCCGTAGCCCTGCGCCCCCTTCTGTGGCTGGATGGGGAGACAGGTCAAGGGCCCCCACCCCTCT  
 CCAGCCCTGCAGCAATGACTACTGCACCTGGACAGCCCTCTCTTTCTAGAGTCTATTTATATTGTCAATTTATAAC  
 ACTCTAGCCCCCTGCTTATTTGGGGACAGATGGTCCCTGTCTGCGGGGTGGCCCTGGCAGAACCACTGCTGAAGAAC  
 CAGGTTCCCTGCGCGGTGAGCGCAGCCCCAGCCCCCTGCTCGAGTTAGTTTACAATTAACATTTGCTTTG  
 TTTGTG

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Fig. 11F

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CGAAGCCACAGCCCGAGCCCGAGCCCGGCGCCACCGCGCCCGGCGCATGGCTTTTGCCCAATTTCCGCC  
 GCATCCTGCGCTGTCTACCTTCGAGAGAGAAAGTCCCGGAATATGAGCACGTCCGCCGACCTGGACCCCAACGAG  
 GTGTGGGAGATCGTGGCGAGCTGGGCGACGGCGCTTCGGCAAGGTTTACAAGGCCAAGAAATAAGGAGACGGGTGCTTT  
 GGCTGGGCCCCAAAGTCAATTGAACCAAGAGTGAGGAGGAGCTGGAGGACTACATCGTGGAGATTGAGATCCTGGCCACCT  
 GCGACCAACCCCTACATTGTGAAGCTCCTGGAGCCTACTATCACGACGGGAAGCTGTGGATCATGATTGAGTTCTGTCCA  
 GGGGAGCCGTGGACGCCATCATGCTGGAGCTGGACAGAGGCCCTCACGGAGCCCCAGATACAGGTGGTTTGCCGCCAGAT  
 GCTAGAAAGCCCTCAACTTCCTGCACAGCAAGAGGATCATCCACCGAGATCTGAAGCTGGCAACGTGCTGATGACCCCTCG  
 AGGGAGACATCAGGCTGGCTGACTTTGGTGTGCTGCTGCCAAGAACTCTGAAGACTCTACAGAAACGAGATTCTTCATCGGC  
 ACGCCTTACTGGATGGCCCCCGAGGTGGTCAATGTGTGAGACCATGAAGACACGCCCTACGACTACAAAGCCGACATCTG  
 GTCCCTGGGCATCACGCTGATTGAGATGGCCCCAGATCGAGCCGCCACACCGAGCTCAACCCCATGCGGGTCTCTGCTAA  
 AGATCGCCAAAGTCGGAACCTCCACGCTGCTCACGCCCTCCAAAGTGGTCTGTAGAGTTCCGTGACTTCTCTGAAGATAGCC  
 CTGGATAAGAACCCAGAACCCGACCCAGTGCCCGCGAGCTGCTGGAGCATCCCTTCTGTCAGCAGCATCACCAAGTAACAA  
 GGCTCTGCGGGAGCTGGTGGCTGAGGCCAAGGCCGAGGTGATGGAAAGAGATCGAAGACGGCCGGGATGAGGGGGAAGAGG  
 AGGACGCCGTGGATGCCGCTCCACCTGGAGAACCATACTCAGAACTCCTCTGAGGTGAGTCCGCCAAGCCTCAATGCT  
 GACAAAGCCTCTCGAGGAGTCACTTCCACCCCGCTGGCACCCAGCCAGTCTCAGGACAGTGTGAATGAGCCCTGCAGCCA  
 GCCCTCTGGGGACAGATCCCTCCAAACCAACAGTCCCGCCAGTCTGTGGCCCTTGGAATGAGAACGGCCTGGCAGTGCCTG  
 TGCCCTGCGGAAGTCCCGACCCGTGTCAATGGATGCCAGAAATTCAGGTAGCCAGGAGCAAGTTGCTGAGCAGGCT  
 GGGACCTCAGCCCAAGCCCAACAGATCTCAAAAGGCCAGCCAGAGCCGGCCCAACAGCAGCGCCCTGGAGACCTTGGG  
 TGGGGAGAAGCTGGCCCATGGCAGCTGGAGCCACCTGCCAGGCAGCTCCAGGGCCTTCCAAGAGGGACTCGGACTGCA  
 GCAGCCTCTGCACCTCTGAGAGCATGGACTATGGTACCCTTCTCCACTGACCTGCTGCTGAACAAGAGATGGGCTCT  
 CTGTCCATCAAGGACCCGAACTGTACAAAACCCCTCAAGCGGACACGCAAAATTTGTGTGGATGGTGTGGAGGTGAG  
 CATCACCACTCCAAGATCATCAGCGAAGATGAGAAAGAGGATGAGGAGATGAGATTCTCAGGCGCCAGGAACTCCGAG  
 AGCTTCGGCTGCTCCAGAAAGAGCATCGGAACCAAGACCCAGCTGAGTAACAAGCATGAGCTGCACTGAGCAATG  
 CATAACGTTTTTGAACACAGGAAATCAACGCCCAAGAGAAGTTCTTTGACACCGGAATTAGAGAACCTGGAGCGTCAAGCAAAA

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Fig. 11G



**Fig. 11H**

STLK6_h	-----MSL	D	C	F	C	T	S	R	T	Q	V	E	S	L	R	P	E	K	Q	S	E	T	S	I	H	Q	Y	L	V	D	E	P	T	L	S	W	S	R	41															
STLK5_h	-----																																						0															
SPAK_h	MAEP	S	G	S	P	V	H	V	Q	L	P	Q	A	A	P	V	T	A	A	A	A	A	P	A	A	T	A	A	P	A	A	P	A	P	A	P	A	P	A	50														
STLK6_h	P	S	T	R	A	S	E	-	V	L	C	S	T	N	V	S	H	Y	E	L	Q	V	E	I	G	R	G	F	D	N	L	T	S	V	H	L	A	R	H	T	P	T	G	T	L	V	T	I	K	I	90			
STLK5_h	-----																																														9							
SPAK_h	P	A	Q	A	V	G	W	P	I	C	R	D	A	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	95						
STLK7_h	-----																																														35							
STLK6_h	T	N	L	E	N	C	N	E	E	R	L	K	A	L	Q	K	A	V	I	L	S	H	F	F	R	H	P	N	I	T	T	Y	W	T	V	E	T	V	G	S	W	L	W	V	I	S	P	F	M	A	140			
STLK5_h	I	N	L	E	A	C	S	N	E	M	V	T	S	-	C	R	A	S	C	M	F	Q	T	L	N	H	P	N	I	V	P	Y	R	A	T	L	I	A	D	N	E	L	W	V	V	T	S	F	M	A	58			
SPAK_h	I	N	L	E	K	C	Q	T	S	M	D	E	L	L	K	E	I	I	Q	A	M	S	Q	C	-	S	H	P	N	V	T	Y	T	S	F	V	V	K	D	E	L	W	L	V	M	K	L	L	S	144				
STLK7_h	I	N	L	E	K	C	Q	T	S	M	D	E	L	L	K	E	I	I	Q	A	M	S	Q	C	-	H	H	P	N	I	V	S	Y	T	S	F	V	V	K	D	E	L	W	L	V	M	K	L	L	S	84			
STLK6_h	Y	G	S	A	S	Q	L	L	R	T	Y	F	P	E	G	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	184		
STLK5_h	Y	G	S	A	K	D	L	I	C	T	H	F	M	D	G	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	102				
SPAK_h	G	G	S	M	L	D	I	I	K	Y	I	V	N	R	G	E	H	K	N	G	V	L	E	E	A	I	I	A	T	I	L	K	E	V	L	E	G	L	D	Y	L	H	R	N	G	Q	I	H	R	D	194			
STLK7_h	G	G	S	V	L	D	I	I	K	H	I	V	A	K	G	E	H	K	S	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	103			
STLK6_h	I	K	A	S	H	I	L	I	S	G	D	G	L	V	T	L	S	G	L	S	H	L	H	S	L	V	K	H	G	Q	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	232	
STLK5_h	V	K	A	S	H	I	L	I	S	V	D	G	K	V	Y	L	S	G	L	R	S	N	L	S	M	I	S	H	G	Q	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	150
SPAK_h	L	K	A	G	N	I	L	L	G	E	D	G	S	V	Q	I	A	D	F	G	V	S	A	F	L	A	T	G	D	V	T	R	N	K	V	R	K	T	E	-	-	-	-	-	-	-	-	-	-	-	-	-	240	

Fig. 12A

**Fig. 12B**

PAK1\_h U51120 MSNNGLDIQDKPPAPPMRNTSTMIGAGSKDAGTLNHGSKPLPPNPEEKKKKDRFYSILP 60  
 PAK4\_h -----  
 PAK5\_h -----  
  
 PAK1\_h U51120 GDKTNKKKKEKERPEISLPSDFEHTTHVGFDAVT-GEFTGMPEQWARLLQTSNITKIS --- 115  
 PAK4\_h ---MFRKKKKRRPEISAPQNFQHRVHTSFDPKEGKFVGLPPQWQNTILD-ILRRPKPVVDP 56  
 PAK5\_h ---MF-GKRIKKRWEISAPSNFEHRVHTGFDQHEDKFTGLPLRQWQSLTEESARRPKPLVDP 56  
  
 PAK1\_h U51120 -----  
 PAK4\_h SRIITRVQIQPMKTVVRGSA MPIVDGYTISGLINDITQKLSVSISSNTLRGRSPTSRRRRAQSLGL 116  
 PAK5\_h ACITSIOTPGAPKTIIVRGSKGAKDGA LLLDEFFENMSVTRSNLSLRDSSPPPARAR --- 112  
  
 PAK1\_h U51120 -----  
 PAK4\_h LGDEHWATDPMYLSQSPQSERTDPHGLYLSGNGGTPAGHKQMPWPEPQSPRVLPINGLAAK 176  
 PAK5\_h -----QENGMPPEEPATTARGGPGK 131  
  
 PAK1\_h U51120 -----  
 PAK4\_h AQSILGPAEFQASQRCQLQLGALC LQSSPBGASPPPTGTNRHGMKA AKHGSEEFARPQSCLVGS 236  
 PAK5\_h AGSRGR-----FAGHSEAGGSGGDRRRAGPEKRPKSSRREGSGGPQESSRDKRP--L SGP 183  
  
 PAK1\_h U51120 LEFY-NSKKTSNSQKYMSTDKS-----AEDYNSSNALNVKA-----VSETPAVPPVS 174  
 PAK4\_h ATGRPGGEGSPSPKTRSSILKRLFRSMFLSTAAATAPSSSKPGPPQSKPNSSERPPQK 296  
 PAK5\_h DVGTTPQAGLASGAKLAAK-----RPFNTYRADTDHPSRGAQGEPHDVAPNGP----- 232

Fig. 13A

PAK1_h	US1120	E	E	D	D	D	D	D	D	A	T	P	P	P	V	I	A	P	R	P	E	H	T	K	S	V	T	R	S	---	---	---	V	I	E	P	L	P	V	T	P	T	R	D	V	A	T	S	P	I	S	P	T	E	N	T	T	230				
PAK4_h		D	N	P	P	S	L	V	A	K	A	O	S	L	P	S	D	Q	P	V	G	T	F	S	P	L	T	S	D	I	S	S	P	Q	K	S	L	R	T	A	P	A	T	G	Q	L	P	G	R	S	S	P	A	G	S	P	R	T	W	H	356	
PAK5_h		---	---	---	---	---	---	---	---	---	---	S	A	G	G	L	A	T	P	O	S	S	S	S	S	S	S	S	S	S	S	R	P	T	R	A	R	G	A	P	S	P	G	V	L	---	---	---	---	---	G	P	H	A	S	E	268					
PAK1_h	US1120	P	---	---	---	---	---	---	---	---	P	D	A	L	T	L	N	T	E	K	Q	K	K	P	K	S	D	E	E	L	E	K	L	R	S	I	V	S	V	G	D	P	K	K	Y	T	R	F	E	K	I	276										
PAK4_h		A	Q	T	S	T	S	N	L	Y	L	P	Q	D	P	T	V	A	K	G	A	---	---	L	A	G	E	D	T	G	V	V	T	H	E	Q	F	K	A	A	L	R	M	V	D	Q	G	D	P	R	L	L	D	S	Y	V	K	I	413			
PAK5_h		P	Q	L	A	P	P	A	-	C	T	P	A	A	P	A	V	P	G	P	P	G	P	R	S	P	O	K	E	P	O	R	V	S	H	E	Q	F	R	A	A	L	Q	L	V	V	D	P	G	D	P	R	S	Y	L	D	N	F	I	K	I	327
PAK1_h	US1120	G	Q	G	A	S	G	T	V	Y	T	A	M	D	V	A	T	G	Q	E	V	A	I	K	Q	M	N	L	Q	Q	Q	P	K	K	E	L	T	I	N	E	I	V	M	R	E	N	K	N	P	N	I	V	N	Y	L	D	S	Y	L	V	336	
PAK4_h		G	E	G	S	T	G	I	V	C	L	A	R	E	H	S	G	R	Q	V	A	V	K	M	M	D	L	R	K	Q	Q	R	R	E	L	L	F	N	E	V	I	M	R	D	Y	Q	H	E	N	V	V	E	M	Y	K	S	Y	L	V	473		
PAK5_h		G	E	G	S	T	G	I	V	C	I	A	T	V	R	S	S	G	K	L	V	A	V	K	K	M	D	L	R	K	Q	Q	R	R	E	L	L	F	N	E	V	I	M	R	D	Y	Q	H	E	N	V	V	E	M	Y	N	S	Y	L	V	387	
PAK1_h	US1120	G	D	E	L	W	V	V	M	E	Y	L	A	G	G	S	L	T	D	V	T	E	T	C	M	D	E	G	Q	I	A	A	V	C	R	E	C	L	Q	A	L	E	S	L	H	S	N	Q	V	I	H	R	D	I	K	S	D	N	I	L	396	
PAK4_h		G	E	E	L	W	V	L	M	E	F	L	Q	G	G	A	L	T	D	I	V	S	Q	V	R	L	N	E	E	Q	I	A	T	V	C	E	A	V	L	Q	A	L	A	L	H	A	Q	G	V	I	H	R	D	I	K	S	D	S	I	L	533	
PAK5_h		G	D	E	L	W	V	V	M	E	F	L	E	G	G	A	L	T	D	I	V	T	H	T	R	M	N	E	E	Q	I	A	A	V	C	L	A	V	L	Q	A	L	S	V	L	H	A	Q	G	V	I	H	R	D	I	K	S	D	S	I	L	447
PAK1_h	US1120	L	G	M	D	G	S	V	K	L	I	D	F	G	F	C	A	Q	I	T	P	E	Q	S	K	R	S	T	M	V	G	T	P	Y	W	M	A	P	E	V	N	T	R	K	A	Y	G	P	K	V	D	I	W	S	L	G	I	M	A	I	E	456
PAK4_h		L	T	L	D	G	R	V	K	L	S	D	F	G	F	C	A	Q	I	S	K	D	V	P	K	R	K	S	L	V	G	T	P	Y	W	M	A	P	E	V	I	S	R	S	I	Y	A	T	E	V	D	I	W	S	L	G	I	M	V	I	E	593
PAK5_h		L	T	H	D	G	R	V	K	L	S	D	F	G	F	C	A	Q	I	S	K	E	V	P	R	R	K	S	L	V	G	T	P	Y	W	M	A	P	E	L	I	S	R	L	P	Y	G	P	E	V	D	I	W	S	L	G	I	M	V	I	E	507
PAK1_h	US1120	M	I	E	G	E	P	P	Y	L	N	E	N	P	L	R	A	L	Y	I	A	T	N	G	T	P	E	L	Q	N	P	E	K	L	S	A	T	E	R	D	F	L	N	R	C	L	E	M	D	V	E	K	R	G	S	A	K	E	L	L	516	
PAK4_h		M	V	D	G	E	P	P	Y	F	S	D	S	P	V	Q	A	M	K	R	L	R	D	S	P	P	P	K	L	K	N	S	H	K	V	S	P	V	L	R	D	F	L	E	R	M	L	V	R	D	P	Q	E	R	A	T	A	Q	E	L	L	653
PAK5_h		M	V	D	G	E	P	P	Y	F	N	E	P	P	L	R	A	M	K	I	R	D	N	I	P	P	R	L	K	N	I	H	K	V	S	P	S	L	K	G	F	L	D	R	L	V	R	D	P	A	Q	R	A	T	A	E	L	L	567			

Fig. 13B

545  
681  
591

PAK1_h	U51120	Q	H	Q	F	L	K	I	A	K	P	S	S	L	T	P	L	I	A	A	K	E	A	T	K	N	V	H
PAK4_h		D	H	P	F	L	Q	T	G	P	E	G	L	V	P	L	I	Q	L	Y	R	K	Q	T	S	T	C	
PAK5_h		K	H	P	F	L	K	A	G	P	P	A	S	V	P	L	R	Q	N	R	T	R						

 RESIDUES THAT MATCH THE CONSENSUS NAMED CONSENSUS #1 EXACTLY.


 BOX RESIDUES THAT MATCH THE CONSENSUS EXACTLY.

Fig. 13C

ZC4_h.pro	MAGPGGWRDREVTDLGHLPDPTGIFSLDKTIIGLGTYGRIYGLHEKTGAF	50
ZC1_h.pro	MAINDSPAKSLVDIDLSSLRDPAGIFEELVEVVGNGITYGVYKGRHVKTGQL	50
ZC4_h.pro	TAVKVMNARKDEEEDLRTELNLLRKYSEHKNIVSFYGAFFKLSPPGQRHQ	100
ZC1_h.pro	AATKVMADVTEDEEEFIKLEINMLKKYSHHNRNIATYYGAFIKKKSPPGHDDIQ	100
ZC4_h.pro	LWMVMELCAGSVTDVVRMTSNQSLKEDWIAIYICREILQGLAHLHAHRVI	150
ZC1_h.pro	LWLVMEFCGAGSITDLVKNTIKGNTLKEDWIAIYISREILRGLAHLHIHVI	150
ZC4_h.pro	HRDIKGNVLLTHNAEVKLVDFGVSAQVSRITNGRRNSFIGTPTYWMAPEVI	200
ZC1_h.pro	HRDIKGNVLLTENAEVKLVDFGVSAQLDRITVIGRRNTTFIGTPTYWMAPEVI	200
ZC4_h.pro	DCDEDPRRSYDYRSVWSVGIATAIEMAEAGAPPLCNLQPLEALFVILRESA	250
ZC1_h.pro	ACDENPDATYDYRSDLWSGCTATAIEMAEAGAPPLCDMHMPRALFLIPRNP	250
ZC4_h.pro	PTVKS SGWSRK FHNFMKCTIKNELERPISANMLQHPFVRDIKNERHVVE	300
ZC1_h.pro	PRLKSKKWSKKFFSFTEGCLVKNYMQRPSTEQLLKHPTIRDPNERIQVRI	300
ZC4_h.pro	SLTRH LTGTIKKR	324
ZC1_h.pro	QLKDHIDRTRKKRGEKDETEYEYSGSEEEVEPEGEPESSIVNVPGES	350
ZC4_h.pro	KVSTLRQALAKRLSPKRRFRAKSSWRPEKLELSDLEARRQRRQRWEDIFN	374
ZC1_h.pro	TLRRDFLRQQENKERSEALRRQQLLQEQLREQEEYKRQLLAERQKRRIE	400
ZC4_h.pro	QHEEELRQVDKDKEDFSSDNDEVFHSIOAEVQIEPLKPYISNPKIEVQE	424
ZC1_h.pro	QQKEQRRLREEQQRREARRRQQREREQRREQEEKRRLEELEERRRKEEE	450

Fig. 14A

ZC4_h.pro	RSPSPNNQDHAHVKESSVPORSILEQAQKPIDIRQRSSQNRQNWLA	474
ZC1_h.pro	RRRAEEKRRVEREQEYIRRQLEEEQRHLEVLLQEQAMLLECRWRE	500
ZC4_h.pro	SGDSKHKILAGKTSYCLTIYISEYKKEEFQEGMNQKCGAQVGLGPEGH	524
ZC1_h.pro	MEEHRQAERLQRQLQEQEAYLLSLQHDHRRPHQHSQQPPPPQERSKPS	550
ZC4_h.pro	CIWQLGESSEFEESPVTGRRSQSSPPYSTIDQKLLVDIHVPDGFVKGIS	574
ZC1_h.pro	FHAPEKAHYEPADRAREVEDFRKTNHSSPEAQSKQTGRVLEPPVPSRS	600
ZC4_h.pro	PPVYLTNEWVGYNALSEIERNDWLTTPAPVIOPEEDGDYVELYDASADTD	624
ZC1_h.pro	ESFSNGNSESVHPALQORPAEQVPVRTTSRSPVLSRRDISPLQSGGQNSQ	650
ZC4_h.pro	GDDDESNDFEEDTYDHANGNDLDNQVDQANDVCKDHDNDNNKFVDDVN	674
ZC1_h.pro	AGQRNSTSIEPRLLWERVEKLVPRPGSGSSGSSNSGSGSHPGSQSGS	700
ZC4_h.pro	NNYYEAPS CPRASVGRDSSCKODGYDGSRGKEEAYRGVGSHTANRSHGGS	724
ZC1_h.pro	GERFRVRS SSKSEGPSQRLENNAVKKPEDKKEVFRPLKPADLTALAKELR	750
ZC4_h.pro	AASEDNAAIGDQEEHAANIGSERRGS EGDGGKGVVRTSEESGALGLNGEE	774
ZC1_h.pro	AVEDVRPPHKVTDYSSSSEESGTTDEEDD DVEQEGADESTS GPEDTRAAS	800
ZC4_h.pro	NLSETDGPGLKRRPASODFEYLLQEEPPGGGNEASNAIDSGAAP SAPDHESDN	824
ZC1_h.pro	SINLSNGETESVKTMIVHDDVES EPAMTPSKEGTLIVRRRTQSA SSTLQKH	850
ZC4_h.pro	KDISESSTOSDFSANHSSPSKSGSMADANFASAILLYAGFVEYPEESPKQ	874
ZC1_h.pro	KSSSFSFTPFIDPRLLQISPSGTTVTTSVVGESCDGMRPE - - AIRQDPTRK	898

Fig. 14B



ZC4_h.pro	PSEVNVNPLYYVSPACKKPLIHMYEKEFTSEICCGSLWGVNLLLGTRSNLY	924
ZC1_h.pro	GSVVNVNPTNTTRPQSDTPEIRKYKRRFNSEILCAALWGVNLLVGTESGLM	948
ZC4_h.pro	LMDRSGKADITKLI RRRPFRQIOVLEPLNLLITISGHNKRLRVYHLTWLR	974
ZC1_h.pro	LIDRS GQGVYP LYNRRRFRQQMDVLEGLNVLTISGKKDKLRVYLSWLR	998
ZC4_h.pro	NKILNNDPESKRRQE- EMLKTEEACKAIDKLTGCEHFSVLQHEFTTYIAI	1023
ZC1_h.pro	NKILHNDPEVEKKQGW T-----TVGDL EGCVHYKVVKYERIKFLVI	1039
ZC4_h.pro	ALKSSIHLIYAWAPKSEFDESTAIKVFEPTLDHKPVTVDLAIGSEKRLKTEES	1073
ZC1_h.pro	ALKSSVEVYAWAPKPYHKFMAFKSEFGEIVHKPPLLVDLTVEEGQRLKVIYG	1089
ZC4_h.pro	SADGYHLIDAESVMSDVTL PKNPLELITIPONITILPDCLGIGMMLTFNA	1123
ZC1_h.pro	SICAFH AVIDVDSGSVYDIYLPTHIQCSIKPHAIILPNTDGMELLVCYED	1139
ZC4_h.pro	EALSV EANEQLFKKILEMWKDIPSSIAFECTQRTTIGWGQKAI EVRSLSQR	1173
ZC1_h.pro	EGVYVNTYGRITKDVVLQW GEMPTSVAYIRSNQTMGWGEKAI EIRSVETG	1189
ZC4_h.pro	VLESELKRRSJKKLRFLCTIRGDKLFFETSLRNHH SRVYFMT LGKLEELQS	1223
ZC1_h.pro	HL DGVFMHKRAQR LKFLCERNDKVFFASVRS GGS SQVYFMTLGR TSLLSW	1239
ZC4_h.pro	NYDV	1227
ZC1_h.pro		1239

 BOX RESIDUES THAT MATCH ZC4\_h.pro EXACTLY.

Fig. 14C

```

Db = LOK1_m
Qy = GEK2_h
*****
Db 1MAFANFRRIILRLSTFEKRRKSREYEHVRRDLDPNDVWEIVGELGDGAFGKVYKAKNKETGA 60
Qy 1MAFANFRRIILRLSTFEKRRKSREYEHVRRDLDPNEVWEIVGELGDGAFGKVYKAKNKETGA 60

*****
Db 61LAAAKVIEETKSEEELEDYIVEIEILATCDHPYIVKLLGAYYDGGKLWIMIEFCPGGAVDA 120
Qy 61LAAAKVIEETKSEEELEDYIVEIEILATCDHPYIVKLLGAYYHDGKLWIMIEFCPGGAVDA 120

*****
Db 121IMLELDRGLTEPQIQVVCRCRQMLEALNFLHGKRRIIHRDLKAGNVLMTLEGDIRLADFGVSA 180
Qy 121IMLELDRGLTEPQIQVVCRCRQMLEALNFLHSKRRIIHRDLKAGNVLMTLEGDIRLADFGVSA 180

*****
Db 181KNLKTLLQKRDSFIGTPYWWMAPEVVLCETMKDAPYDYKADIWSLGITLIEMAQIEPPHHEL 240
Qy 181KNLKTLLQKRDSFIGTPYWWMAPEVVMCETMKDTPDYKADIWSLGITLIEMAQIEPPHHEL 240

*****
Db 241NPMRVLLKIAKSDPPTLLTPSKWSVEFRDFLKIADLKNPETRPSAAQLLQHPFVSRVTSN 300
Qy 241NPMRVLLKIAKSDPPTLLTPSKWSVEFRDFLKIADLKNPETRPSAAQLLEHPFVSSITSN 300

*****
Db 301KALRELVAEAKAEVMEIEEDGREDEGEEDAVDAPPLVNHTQDSANVTQPSLDSNKLQD 360
Qy 301KALRELVAEAKAEVMEIEEDGREDEGEEDAVDAASTLENHTQNSSEVSPPSLNADKPLEE 360

```

Fig. 15A

```

* * * * * . . . . . * * * * * . . . . . * * * * *
Db 361 S-STPLPPSQPEVNGPCSQPSGQPLQTTSPADGLSKNDNDLKVPVPLRKSRPLSMDA 419
Qy 361 SPSTPLAPSQSQDSVNEPCSQPSGDRSLQTTSPVPVAPGNENGLAVPVPLRKSRPVSMMDA 420

* * * * * . . . . . * * * * * . . . . . * * * * *
Db 420 RIQMDEEKQIPDQDENPSPAASKSQKANQSRPNSSALETLGGEALTNGGLELPSSVTPSH 479
Qy 421 RIQVAQEKQVAEQGGDLSPAANRSQKASQSRPNSSALETLGGEKLANGSLEPPAAAPGP 480

* * * * * . . . . . * * * * * . . . . . * * * * *
Db 480 SKRASDCSNLSTSESMGYGTSLSADLSLNKETGSLSLKGSKLHNKTLKRTRRFVVDGVEV 539
Qy 481 SKRSDCSSLCTSESMGYGTLNSTDLSLNKEMGSLSIKDPKLYKKTLKRTRKFVVDGVEV 540

* * * * * . . . . . * * * * * . . . . . * * * * *
Db 540 SITTSKIISEDEKKDEEMRFLRRQELRELRLQLQKEEHRNQTLSSKHLEQLQMHKRFEQ 599
Qy 541 SITTSKIISEDEKKDEEMRFLRRQELRELRLQLQKEEHRNQTLSSKHLEQLQMHKRFEQ 600

* * * * * . . . . . * * * * * . . . . . * * * * *
Db 600 EINAKKKFYDVELENLERQQKQKQVEKMEQDHSVRRKEEAKRIRLEQDRDYAKFQEQLKQM 659
Qy 601 EINAKKKFFDTELENLERQQKQKQVEKMEQDHAVRRREEARRIRLEQDRDYTRFQEQLKLM 660

* * * * * . . . . . * * * * * . . . . . * * * * *
Db 660 KKEVKSEVEKLPQRQKESMKQKMEEHSQKKQLDRDRDFVAKQKEDLEAMRKLT TENRRE 719
Qy 661 KKEVKNEVEKLPQRQKESMKQKMEEHTQKKQLDRDRDFVAKQKEDLEAMRKLT TDNRRE 720

```

Fig. 15B

```

*****
Db 720 ICDKERDCLSKKQELLRDREAAALWEMEEHQLQERHQLVKQQLKDQYFLQRHDLRLKKHEKE 779
Qy 721 ICDKEREC LMKKQELLRDREAAALWEMEEHQLQERHQLVKQQLKDQYFLQRHELLRKKHEKE 780

*****
Db 780 REQMQRYNQRMMEQLKVRQQQEKARLPKIQRSDDGETRMAMYKKSLSHINGAGSASEQREKI 839
Qy 781 REQMQRYNQRMIEQLKVRQQQEKARLPKIQRSEKTRMAMYKKSLSHINGGSAAEQREKI 840

*****
Db 840 KQFSQQEEKRQKAERLQQQKHEHQMRDMVAQCESNMSELQQQLQNEKCYLLVEHETQKLK 899
Qy 841 KQFSQQEEKRQKSERLQQQKHENQMRDMLAQCESNMSELQQQLQNEKCHLLVEHETQKLK 900

*****
Db 900 ALDESHNQSLKEWRDKLRPRKKALEEDLNQKKREQEMFFKLSEEA-PRPTTPSKASNFF 958
Qy 901 ALDESHNQNLKEWRDKLRPRKKALEEDLNQKKREQEMFFKLSEEAECNPSTPSKAAKFF 960

*****
Db 959 PYSSGDAS 966
Qy 961 PYSSGDAS 968

```

Fig. 15C